NOVARTIS

Clinical Development

LTT462

Oncology Clinical Trial Protocol CLTT462X2101 / NCT02711345

A phase I dose finding study of oral LTT462 in adult patients with advanced solid tumors harboring MAPK pathway alterations

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List of abbreviations

AE	Adverse event
ALK	Anaplastic lymphoma kinase
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase/ glutamic pyruvic transaminase/ GPT
ANC	Absolute neutrophil count
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase/ glutamic oxaloacetic transaminase/ SGOT
AUC	Overall exposure
AUC_{inf}	Total plasma exposures
BHLRM	Bayesian hierarchical Logistic Regression Model
BID	*Bis in diem*/twice a day
BLRM	Bayesian Logistic Regression Model
BRAF	v-raf murine sarcoma viral oncogene homolog B1
BUN	Blood urea nitrogen
BVN	Bivariate normal
[redacted]	[redacted]
CK	Creatine kinase, also known as CPK
C_{max}	Maximum concentration
C_{min}	Minimum concentration
CMO&PS	Chief Medical Office and Patient Safety
CNS	Central nervous system
CPK	Creatine phosphokinase, also known as CK
CR	Complete response
CRF	Case report/record form; the term CRF can be applied to either EDC or Paper
CRO	Contract Research Organization
CSR	Clinical study report
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse events
[redacted]	[redacted]
C_{trough}	Concentration at trough
[redacted]	[redacted]
DCR	Disease control rate
DDS	Dose-determining Set
DLT	Dose limiting toxicity
DOR	Duration of response
DUSP6	Dual specificity phosphatase 6
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern cooperative oncology group
eCRF	Electronic case report form
EDC	Electronic data capture
[redacted]	[redacted]
EoT	End of treatment
ERK	Extracellular signal-regulated kinases
EWOC	Escalation with overdose control
FAS	Full analysis set

FDA	Food and Drug Administration
[redacted]	[redacted]
FFPE	Formalin fixed paraffin embedded
FIH	First-in-human
Fpo	Oral bioavailability
GGT	Gamma-glutamyl-transferase
GI	Gastrointestinal
GLP	Good laboratory practice
GTPase	Small guanidine triphosphatase
hCG	Human chorionic gonadotropin
Hgb	Hemoglobin
HGS	High-grade serous
HR	Heart Rate
HRAS	Harvey rat sarcoma viral oncogene homolog
IC_{50}	Inhibition concentration 50%
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IN	Investigator notice
INR	International normalized ratio
[redacted]	[redacted]
IRB	Institutional Review Board
Iv	Intravenous
KRAS	Kirsten rat sarcoma viral oncogene homolog
[redacted]	[redacted]
LDH	Lactate dehydrogenase
[redacted]	[redacted]
[redacted]	[redacted]
LVEF	Left ventricular ejection fraction
MAP	Meta-analytic-predictive
MAPK	Mitogen activated protein kinase
MedDRA	Medical dictionary for regulatory activities
MEK	Mitogen-activated protein kinase kinase
[redacted]	[redacted]
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
MUGA	Multiple gated acquisition
NCI	National Cancer Institute
[redacted]	[redacted]
[redacted]	[redacted]
NRAS	Neuroblastoma RAS viral (v-ras) oncogene homolog
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
ORR	Objective response rate
[redacted]	[redacted]
PAS	Pharmacokinetic analysis set
PD	Pharmacodynamic

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
PFS	Progression free survival
[redacted]	[redacted]
PHI	Protected Health Information
[redacted]	[redacted]
[redacted]	[redacted]
PPI	Proton pump inhibitors
PR	Partial response
[redacted]	[redacted]
PT	Prothrombin time
[redacted]	[redacted]
[redacted]	[redacted]
QD	Once daily
RAP	The Report and Analysis Plan (RAP) is a regulatory document which provides evidence of preplanned analyses
RDE	Recommended dose for expansion
RDI	Relative dose intensity
REB	Research Ethics Board
RECIST	Response evaluation criteria in solid tumors
RVO	Retinal vein occlusion
SAE	Serious Adverse Event
SD	Stable disease
[redacted]	[redacted]
STL	Standard tables listings
SUSAR	Suspected unexpected serious adverse reactions
T½	Half-life
[redacted]	[redacted]
[redacted]	[redacted]
ULN	Upper limit of normal
[redacted]	[redacted]

Glossary of terms

Assessment	A procedure used to generate data required by the study
Biologic Samples	A biological specimen including, for example, blood (plasma, serum), saliva, tissue, urine, stool, etc. taken from a study subject or study patient
Cohort	A group of newly enrolled patients treated at a specific dose and regimen (i.e. treatment group) at the same time
Cycles	Number and timing or recommended repetitions of therapy are usually expressed as number of days (e.g. q28 days)
Dose level	The dose of drug given to the patient (total daily or weekly etc.)
Enrollment	Point/time of patient entry into the study; the point at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol)
Investigational drug	The study treatment whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with "investigational new drug."
Investigational treatment	Drug whose properties are being tested in the study as well as their associated placebo and active treatment controls (when applicable). This also includes approved drugs used outside of their indication/approved dosage, or that are tested in a fixed combination. Investigational treatment generally does not include other study treatments administered as concomitant background therapy required or allowed by the protocol when used in within approved indication/dosage
Medication number	A unique identifier on the label of each study treatment package which is linked to one of the treatment groups of a study
Other study treatment	Any drug administered to the patient as part of the required study procedures that was not included in the investigational treatment
Subject Number (Subject No.)	A unique identifying number assigned to each subject who enrolls in the study
Period	A subdivision of the study timeline; divides stages into smaller functional segments such as screening, baseline, titration, washout, etc.
Stage related to study timeline	A major subdivision of the study timeline; begins and ends with major study milestones such as enrollment, randomization, completion of treatment, etc.
Stage in cancer	The extent of a cancer in the body. Staging is usually based on the size of the tumor, whether lymph nodes contain cancer, and whether the cancer has spread from the original site to other parts of the body
Stop study participation	Point/time at which the patient came in for a final evaluation visit or when study treatment was discontinued whichever is later
Study treatment	Includes any drug or combination of drugs in any study arm administered to the patient (subject) as part of the required study procedures, including placebo and active drug run-ins. In specific examples, it is important to judge investigational treatment component relationship relative to a study treatment combination; study treatment in this case refers to the investigational and non-investigational treatments in combination.
Study treatment discontinuation	Point/time when patient permanently stops taking study treatment for any reason
Supportive treatment	Refers to any treatment required by the exposure to a study treatment, e.g. premedication of vitamin supplementation and corticosteroid for pemetrexed disodium.
Treatment group	A treatment group defines the dose and regimen or the combination, and may consist of 1 or more cohorts. Cohorts are not expanded, new cohorts are enrolled.
Variable	Identifier used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified time points
Withdrawal of Consent	Withdrawal of consent occurs only when a patient does not want to participate in the study any longer, and does not want any further visits or assessments, and does not want any further study related contact

Amendment 3 (13-Mar-2018)

Amendment rationale

The purpose of this amendment is to introduce the following changes into the protocol:

The age of patients eligible for inclusion in this study has been reduced from ≥18 years to ≥12 years to allow access to LTT462 treatment for adolescent patients who have the same risk/benefit as the adult population. [redacted] The inclusion of patients ≥12 years is supported by published literature showing that adolescents have similar toxicity profiles, maximum tolerated doses, and pharmacokinetic parameters compared to adults.

- The following inclusion and exclusion criteria were amended to allow the recruitment of adolescent patients:
  - The informed consent inclusion criterion (inclusion criterion #1) was updated to state that in addition to the assent of any adolescent patients, the signature of at least one parent or guardian is required to allow the adolescent to participate in the trial. This is as per ICH guidelines for recruitment of adolescent patients.
  - The study age inclusion criterion (inclusion criterion #2) was amended to decrease the age of study participation from ≥18 to ≥12 years.
  - The study biopsy inclusion criterion (inclusion criterion #7) was amended to allow adolescent patients to participate in the study without having to provide the required new biopsy at screening or on treatment if not feasible. This will be reviewed by the Investigator and will require written confirmation from Novartis prior to study inclusion.

[redacted]

- Two PK samples have been added on Cycle 1 Day 8 at 2 hours and 4 hours post-dose, for all patients treated with a QD, BID [redacted] to better characterize the PK of LTT462.

[redacted]

This amendment will also clarify any ambiguous protocol language, make minor changes/corrections for consistency, and amend any discrepancies that have been identified.

[redacted]

Changes to the protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underline for insertions.

- Protocol summary, Section 2.2, Section 2.3, Table 3-1, Section 4.1, Section 5.1, Section 5.2: Addition of language to show that the study will recruit both adult and adolescent patients.
- Protocol summary, Section 5.2: Changed age of patients in inclusion criterion #2 from 18 years to ≥12 years to allow recruitment of adolescent patients.

[redacted]

- Section 1.1.3, Section 1.1.4, Section 2.3: addition of supportive information/data for justification for inclusion of adolescent patients in the study.

[redacted]

- Section 5.2: amended inclusion criterion #1 to include that a parent or legal guardian will need to consent for adolescent patients to be included.
- Section 5.2 and Table 7-8: amended inclusion criterion #7 to allow adolescent patients to participate if it is not possible for a new biopsy to be performed at screening or on-treatment. This will be possible only after written agreement between the Investigator and Novartis.

[redacted]

- Section 6.1: Added language to clarify the administration instructions for BID dosing.

- Section 7.2.3.1 and Table 7-6: Clarification of when PK samples should be taken relative to the previous dose of LTT462 and next dose of LTT462.
- Table 7-6: Addition of two PK sampling timepoints on Cycle 1 Day 8 for patients treated with a QD, BID [redacted] off regimen.
- Table 7-8: removal of "if medically feasible" footnote for newly obtained tumor biopsy for biomarker analyses as this and is inconsistent with the inclusion criterion for adult patients. A new footnote applicable to adolescent patients has been added.

[redacted]

- Section 13: Addition of references for adolescent studies.

[redacted]

IRBs/IECs

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC approval prior to implementation.

The changes herein affect the Informed Consent. Sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this protocol amendment.

Amendment 2 (14-Aug-2017)

Amendment rationale

The purpose of this amendment is to introduce the following changes into the protocol:

- Update of the protocol language to allow the exploration of a BID regimen in addition to QD [redacted] that are already included in the protocol. [redacted]

[redacted]

This amendment will further clarify protocol phrases, minor changes/corrections for consistency and correct minor protocol discrepancies that have been identified.

Study Status

The first patient first visit occurred on 15th April 2016. [redacted]

Changes to the protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underline for insertions.

- List of abbreviations, Section 8.2.2 and Section 8.3: Changed name of Drug Safety and Epidemiology department at Novartis to Chief Medical Office and Patient Safety.
- Section 1.2.2.1: addition of information on BID dosing regimen in pre-clinical studies (as already available in the LTT462 Investigator's Brochure).

[redacted]

- Section 2.2, Section 2.3, Section 4.1.1, Table 4-1, Section 4.1.3, Figure 4-1, Section 6.2.3.1, Table 7-1, Section 10.1.4, Section 10.4.2.1, Section 13, Section 14.5.2, Section 14.5.2.2, Section 14.5.2.2.2, Section 14.5.2.2.3, Section 14.5.2.2.4, Section 14.5.2.2.5, Table 14-20, Table 14-21, Table 14-22, Table 14-23: Update of protocol language and statistical sections to allow testing of BID regimen with LTT462.

[redacted]

- Section 6.1.1 and Table 6-1: Update of administration instructions to include BID dosing [redacted]
- Table 7-1, Table 7-5, Section 7.2.3.1, Table 7-6, Section 7.2.4 and Table 7-8: Addition of a new PK and DUSP6 sample time-point at 12 hours on C1D15 to allow the testing of BID regimen with LTT462, and addition of ECG assessments for BID dosing in-line with existing time-points. Clarifications on existing regimens (QD, [redacted]) are made in the tables, but there are no new assessments/samples for these regimens.
- Section 7.2.2.7: Removal of incorrect text.
- Section 11.5: Updated publication policy in line with Novartis standards.

[redacted]

IRBs/IECs and HA Approval

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC approval prior to implementation.

The changes herein affect the Informed Consent. Sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this protocol amendment.

Amendment 1 (14-Jul-2016)

Amendment rationale

This amendment addresses the following revision [redacted]

Additionally, the following revisions have been made:

[redacted]

- Changed inclusion criteria from patient must be willing to undergo required study biopsies (if medically feasible) to patients must have a site of disease amenable to biopsy, and be a candidate for tumor biopsy according to the treating institution's guidelines to be eligible for the study. These biopsies will be taken at screening/baseline and during therapy and used for assessment of secondary [redacted] objectives to answer translational research questions [redacted]

[redacted]

This amendment will further clarify protocol phrases, minor changes/corrections for consistency and correct minor protocol discrepancies that have been identified.

Changes to the protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underline for insertions.

[redacted]

- Protocol Summary and Section 5.2: Revised wording of inclusion criterion 7 to mandate that patients must have site of disease amenable to biopsy, [redacted]

[redacted]

- Section 5.3: Added in exclusion criterion 7 to confirm that any malignant disease other than that being treated in the study is considered a medical condition that would exclude a patient.

[redacted]

[redacted]

IRBs/IECs and HA Approval

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC approval prior to implementation.

The changes herein affect the Informed Consent. Sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this protocol amendment.

Protocol summary

Title	A phase I dose finding study of oral LTT462 in adult patients with advanced solid tumors harboring MAPK pathway alterations
Brief title	N/A
Sponsor and Clinical Phase	Novartis Phase I
Investigation type	Drug
Study type	Interventional
Purpose and rationale	The purpose of this first-in-human (FIH) trial is to characterize safety and tolerability of the ERK1/2 inhibitor LTT462 and identify a recommended dose and regimen for future studies in adult and adolescent patients with advanced solid tumors harboring mitogen activated protein kinase (MAPK) pathway alterations. MAPK pathway is frequently activated in human cancers with *RAS* genes (*KRAS*, *NRAS* and *HRAS*) being the most frequently mutated oncogenes in all cancers (>30%) with *KRAS* mutations being the most prevalent in 20% of all cancers. However, no effective therapies exist for *KRAS* mutant cancers. Inhibitors against BRAF or MEK suppress MAPK signaling and have demonstrated efficacy in *BRAF* mutant tumors, but these effects are almost always short-lived due to multiple acquired resistance mechanisms which commonly reactivate ERK1/2 signaling. In this setting, inhibition of ERK1/2, which are the most distal kinases in the MAPK signaling cascade, effectively inhibits MAPK signaling and demonstrates anti-tumor effects in preclinical studies (Morris et al. 2013). [redacted] Therefore it is expected that the ERK[redacted] inhibitor LTT462 will result in anti-tumor activity in adult and adolescent patients with advanced solid tumors harboring documented MAPK pathway alterations.
Primary Objective(s) and Key Secondary Objective	To characterize safety and tolerability of LTT462 and identify a recommended dose and regimen for future studies in adult and adolescent patients with advanced solid tumors harboring MAPK pathway alterations.
Secondary Objectives	To evaluate the preliminary anti-tumor activity of LTT462 To evaluate the pharmacokinetic (PK) profile of LTT462 To assess the pharmacodynamic (PD) effect of LTT462
Study design	This study has been designed as a Phase I, open-label, dose finding study with a dose escalation part and a dose expansion part in adult and adolescent patients with advanced solid tumors harboring documented MAPK pathway alterations. The study treatment, LTT462, will be taken until patient experiences unacceptable toxicity, progressive disease and/or treatment is discontinued at the discretion of the investigator or the patient or due to withdrawal of consent. [redacted] A cycle is defined as 28 days.
Population	The dose escalation part of the study will be conducted in adult and adolescent patients with advanced solid tumors harboring MAPK pathway alterations. [redacted]
Inclusion criteria	1. Able to understand and voluntarily sign the ICF and ability to comply with the study visit schedule and the other protocol requirements. 2. Patient (male or female) ≥12 years of age 3. Must have progressed following standard therapy, or for whom, in the opinion of the Investigator, no effective standard therapy exists, is tolerated or appropriate. 4. ECOG (Eastern cooperative oncology group) performance status ≤1 5. Presence of at least one measurable lesion according to RECIST v1.1. [redacted]

	Dose escalation part: Patients must have advanced solid tumors harboring at least one of the MAPK pathway alterations. [redacted] 7. Patients must have a site of disease amenable to biopsy and be a candidate for tumor biopsy. Patients must be willing to undergo a new tumor biopsy [redacted].
Exclusion criteria	1. Prior treatment with ERK inhibitors. 2. History or current evidence of retinal vein occlusion (RVO) or current risk factors for RVO. 3. Any medical condition that would, in the investigator's judgment, prevent the patient's participation in the clinical study due to safety concerns or compliance with clinical study procedures. [redacted] 5. Patients receiving proton pump inhibitors (PPI) which cannot be discontinued 3 days prior to the start of study treatment and for the duration of the study. 6. Clinically significant cardiac disease [redacted]
Investigational and reference therapy	LTT462
Efficacy assessments	Tumor assessment per RECIST v1.1
Safety assessments	**Safety:** ● Incidence and severity of adverse events (AEs) and serious AEs, including changes in laboratory values, vital signs, electrocardiograms (ECGs) and cardiac imaging, and ophthalmological assessments. ● Incidence and nature of dose limiting toxicities (DLTs; dose escalation only) **Tolerability:** Dose interruptions, reductions, and dose intensity
Other assessments	Plasma concentrations and derived PK parameters of LTT462 Changes from baseline of PD markers in tumor tissue (DUSP6) and in blood (DUSP6).
Data analysis	The statistical analysis of the safety and tolerability primary endpoints other than incidence of DLTs (during the dose escalation part) will be descriptive, no hypotheses or models will be considered. Incidence of DLTs during the dose escalation part will

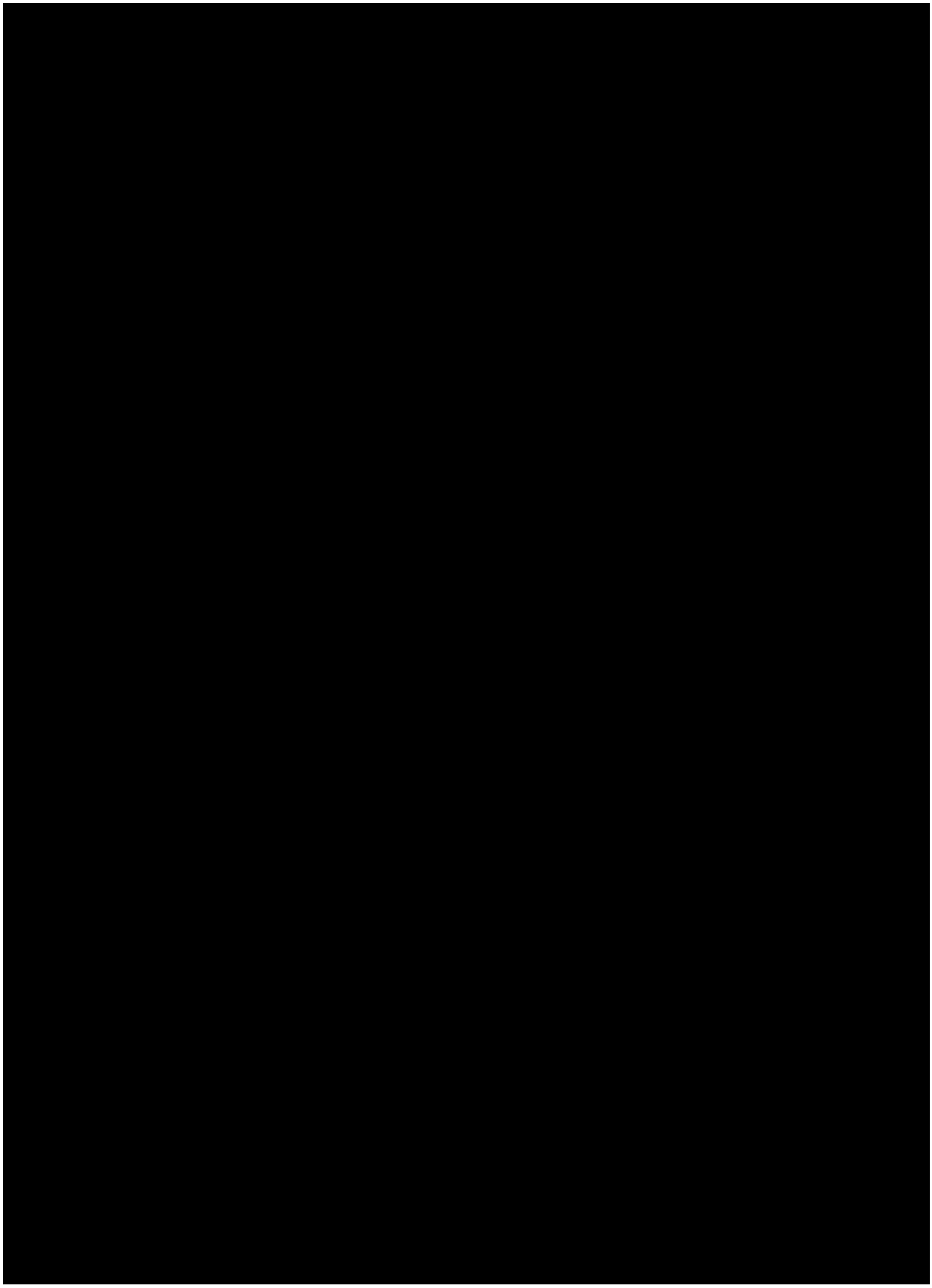
	be analyzed using a Bayesian hierarchical logistic regression model (BHLRM), which is a hierarchical adaptation of the Bayesian logistic regression model (BLRM).
Key words	LTT462, ERK, MAPK alterations, KRAS, BRAF, solid tumor, BHLRM, BLRM.

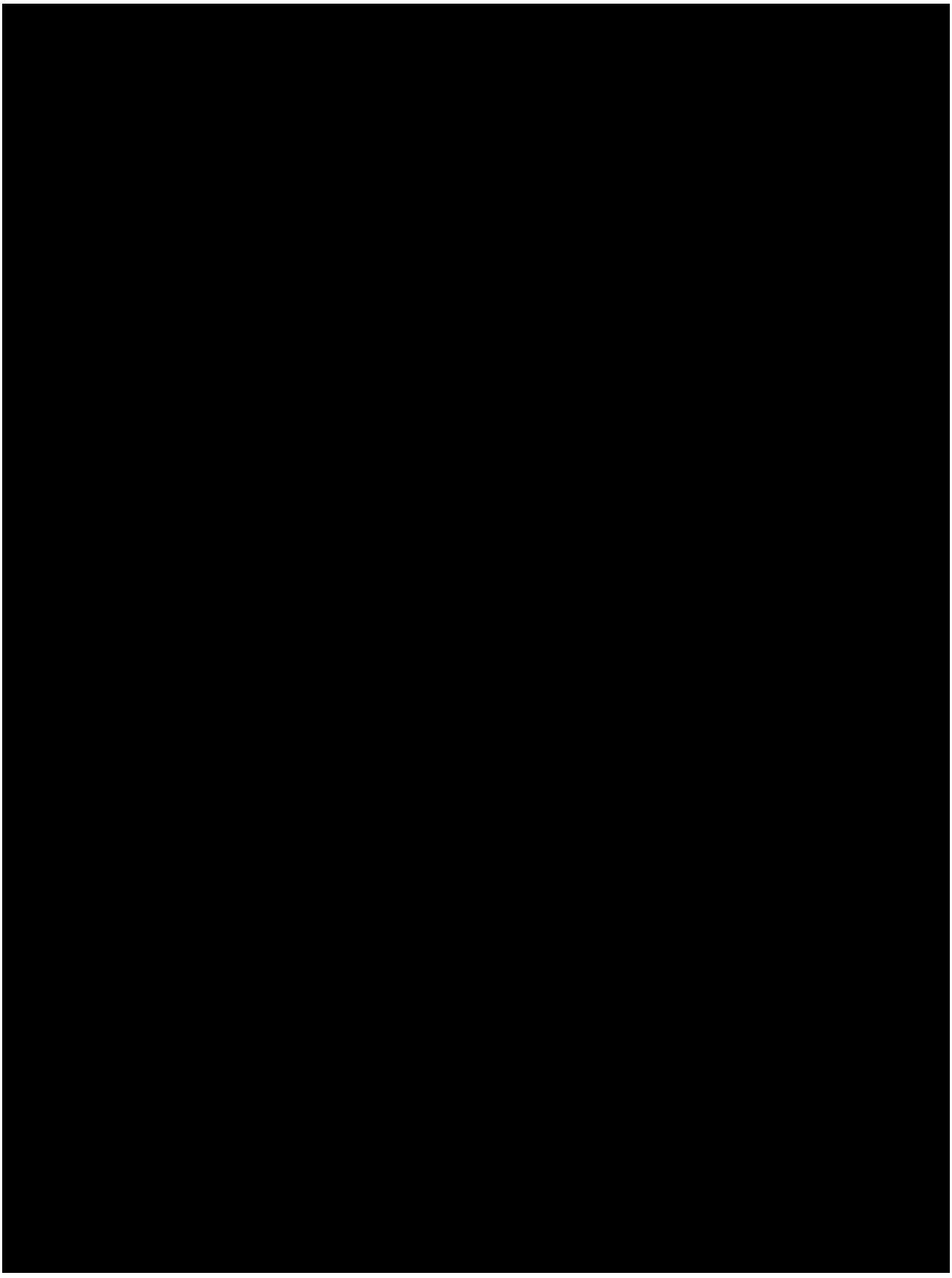
1 Background

1.1 Overview of disease pathogenesis, epidemiology and current treatment

The RAS/RAF/MEK/ERK or MAPK (mitogen activated protein kinase) pathway is a key signaling cascade that drives cell proliferation, differentiation, and survival. Dysregulation of this pathway underlies many instances of tumorigenesis (Kirkwood et al 2012). This pathway is comprised of the RAS small guanidine triphosphatase (GTPase), which, when activated, promotes the activation of the RAF family proteins. Activated RAF proteins lead to the phosphorylation and activation of mitogen-activated protein kinase kinase (MEK) 1/2 proteins, which subsequently phosphorylate and activate extracellular signal-regulated kinases (ERKs). ERKs phosphorylate a variety of substrates including multiple transcription factors, and regulate several key cellular activities, including proliferation, differentiation, migration, survival and angiogenesis. Aberrant signaling or inappropriate activation of the MAPK pathway has been shown in multiple tumor types, including melanoma, lung, ovarian and pancreatic cancer, and can occur through several distinct mechanisms, including activating mutations in *RAS* and v-raf murine sarcoma viral oncogene homolog B1 (*BRAF)* (Lea et al 2007).

The MAPK pathway is frequently mutated in human cancer. Kirsten rat sarcoma viral oncogene homolog (*KRAS)* and *BRAF* mutations occur most frequently, appearing in approximately 30% of human cancers (reviewed in Zhao and Adjei 2014). *RAS* genes (*KRAS*, neuroblastoma RAS viral (v-ras) oncogene homolog (*NRAS)* and Harvey rat sarcoma viral oncogene homolog (*HRAS*)) are mutated in numerous cancer types, including colorectal (50%), melanoma (20%), lung (19%), ovarian (18%) and pancreatic (90%) cancers. *BRAF* is mutated in melanoma (50%), thyroid (50%), low grade ovarian (36%) and colorectal (9%) cancers, with $BRAF^{V600E}$ accounting for greater than 90% of observed mutations in *BRAF* gene cancer (Cantwell-Dorris et al 2011). Although selective, BRAF and, to a lesser extent, MEK inhibitors have demonstrated clinical activity in *BRAF*-mutant tumors. However, there are currently no effective therapies for *KRAS*-mutant tumors (Cantwell-Dorris et al 2011). ERK1/2 is the most distal kinase in the MAPK signaling cascade and they are an attractive drug target to effectively suppress oncogenic MAPK signaling and cancer cell proliferation.



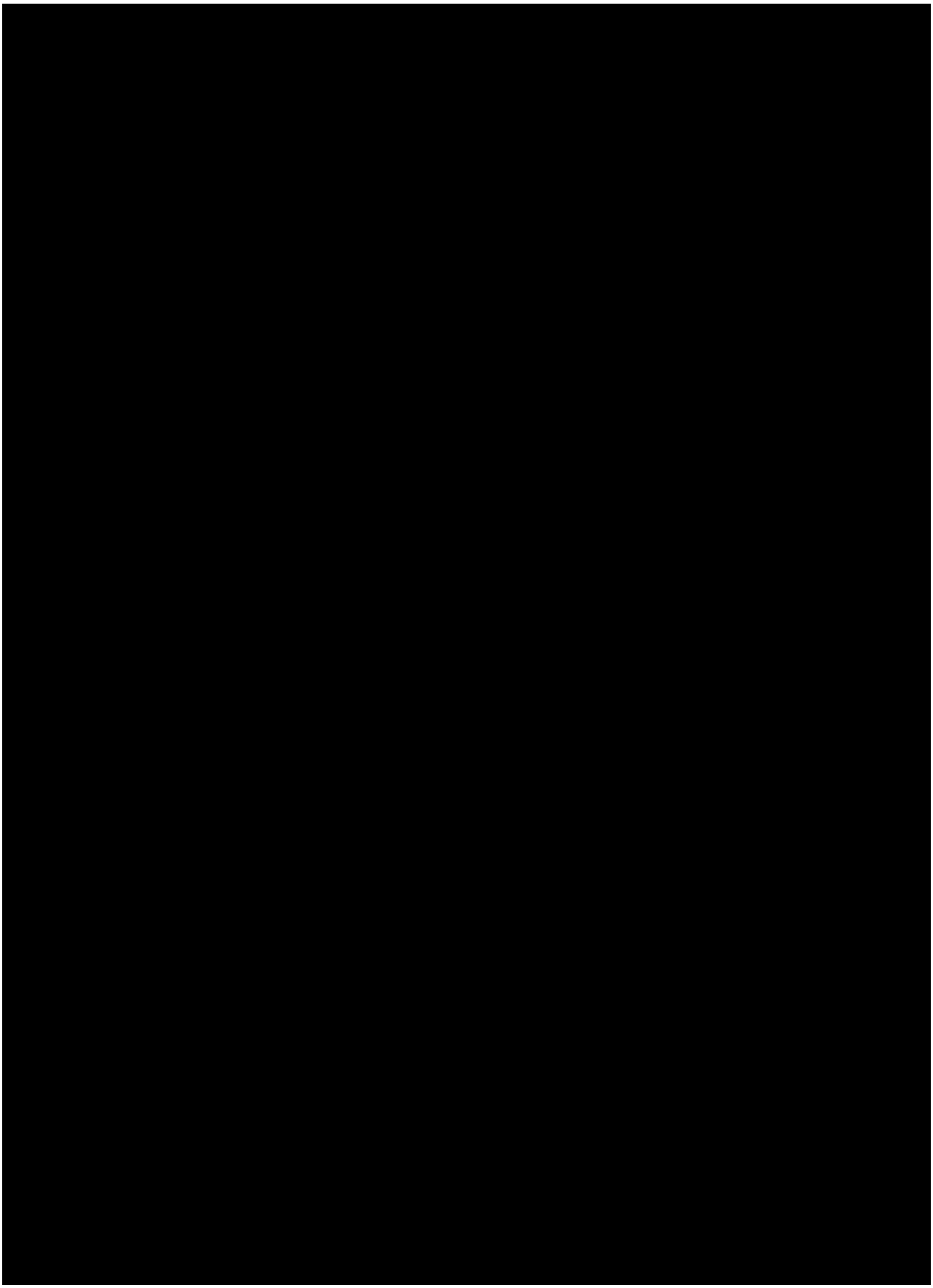


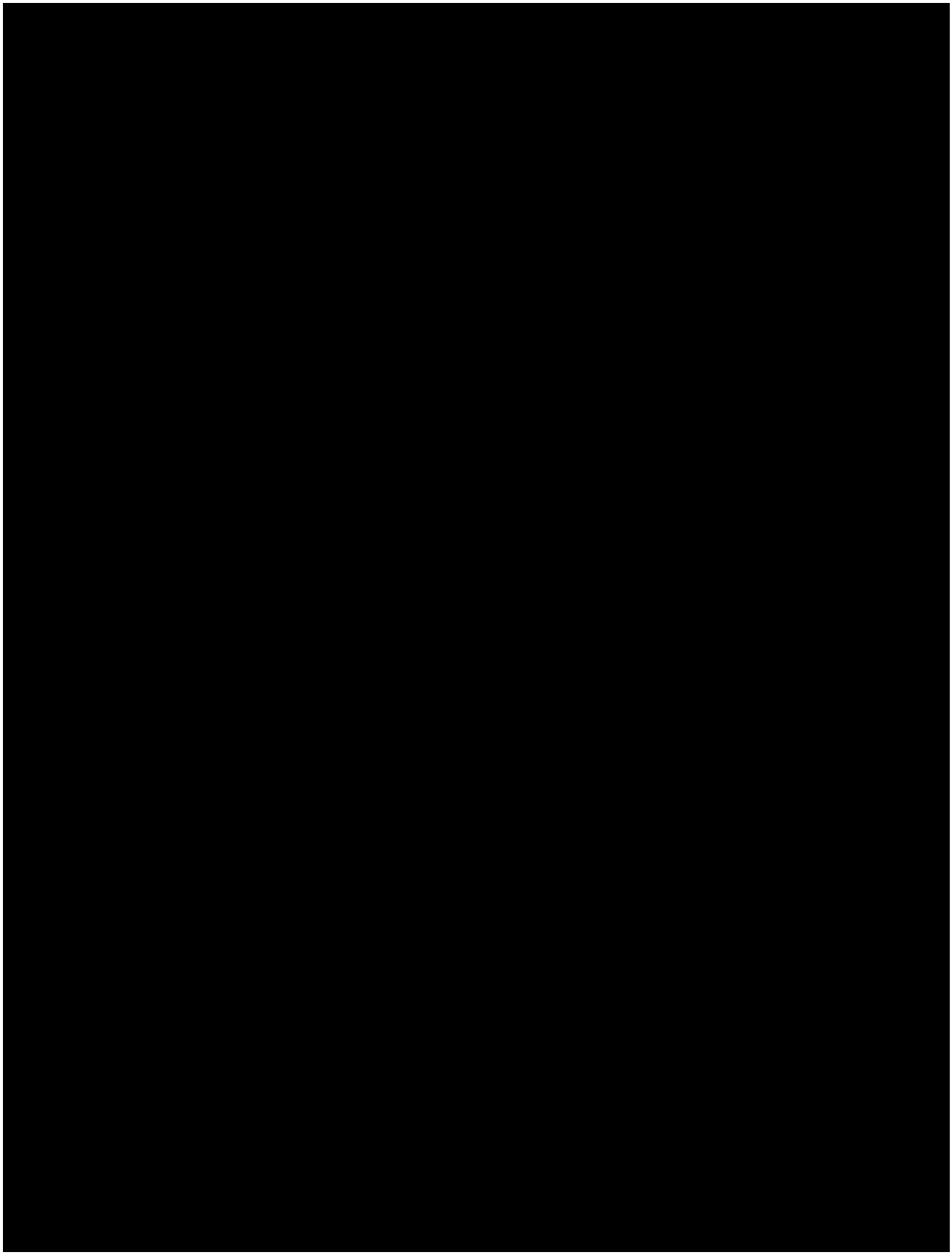
[redacted]

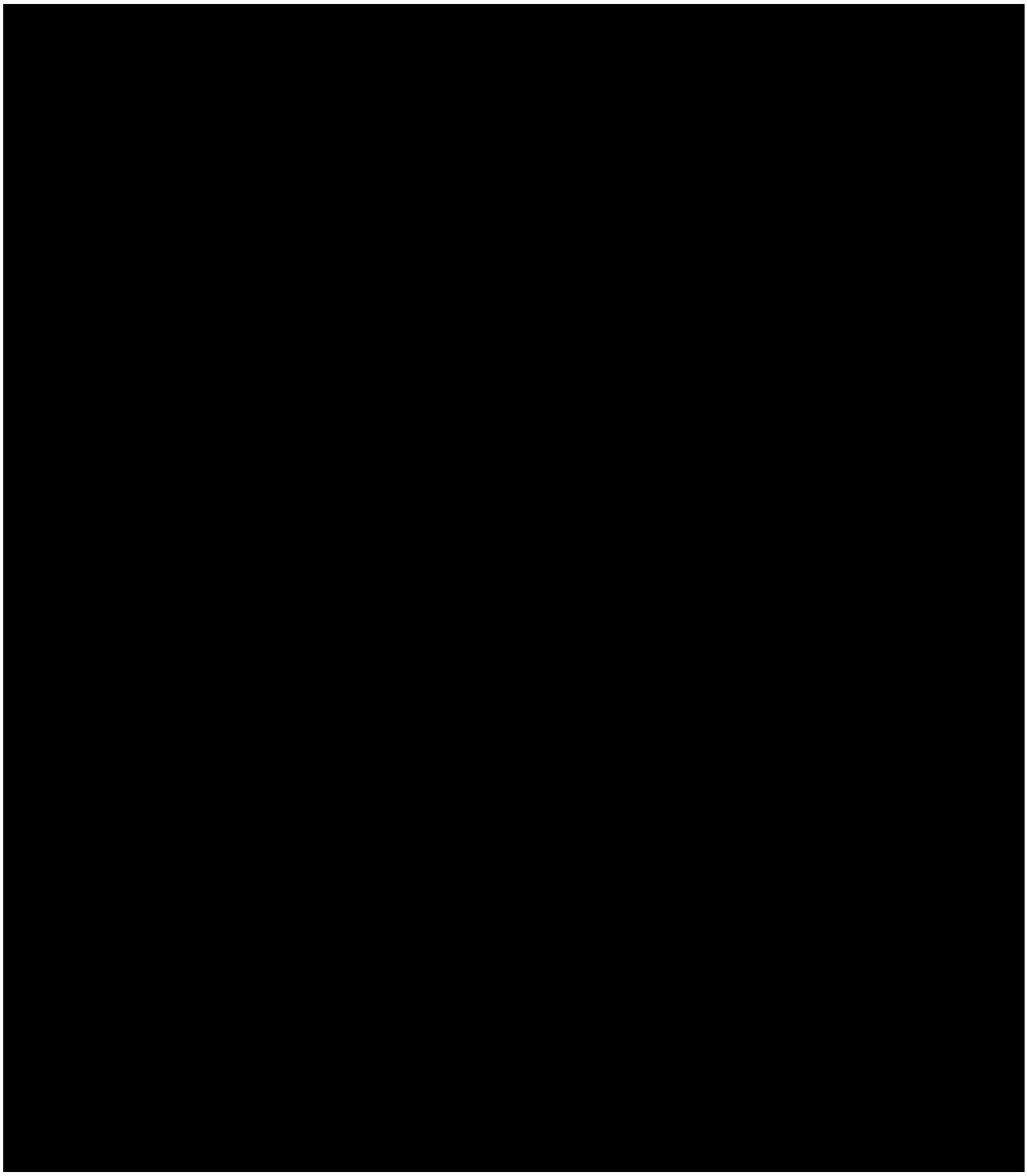
1.2 Introduction to investigational treatment

1.2.1 Overview of LTT462

LTT462 is a potent and selective, orally bioavailable, [redacted] ERK[redacted] inhibitor. [redacted]







[redacted]

1.2.3 Clinical experience

In addition to LTT462X2101 (the first-in-human (FIH) study described in this protocol), LTT462 is currently being tested in [LXH254X2102] a Phase Ib, open-label, multicenter study of oral LXH254 [redacted] in combination with oral LTT462 in adult patients with advanced or metastatic KRAS or BRAF mutant Non-Small Cell Lung Cancer.

1.2.3.1 Clinical Safety

For LTT462x2101, the first patient first visit occurred on 15th April 2016. [redacted]

[redacted]

In the ongoing clinical study LXH254X2102, the first patient first visit occurred on 24th February 2017. [redacted]

2 Rationale

2.1 Study rationale and purpose

MAPK pathway is frequently activated in human cancers. The *RAS* genes, including *KRAS*, *NRAS* and *HRAS*, are the most frequently mutated oncogenes in all cancers (>30%) with *KRAS* mutations being the most prevalent in 20% of all cancers, such as in pancreatic (90%), colorectal (40%), and lung (30%) cancers. However, no effective therapies exist for *KRAS* mutant cancers, largely because KRAS itself has proven difficult to target directly with small molecules (Young et al 2009). Inhibitors against BRAF or MEK suppress MAPK signaling and have demonstrated efficacy in *BRAF* mutant tumors; nonetheless these effects are almost always short-lived due to multiple acquired resistance mechanisms which commonly reactivate ERK[redacted] signaling. In this setting, inhibition of ERK[redacted], which are the most distal kinases in the MAPK signaling cascade, effectively inhibits MAPK signaling and demonstrates anti-tumor effects in preclinical studies (Morris et al 2013). [redacted]

2.2 Rationale for the study design

The design of the phase I, open label, dose finding study, with a dose escalation part and a dose expansion part, was chosen in order to establish the safety and tolerability of LTT462 and identify a recommended dose and regimen for future studies in adult and adolescent patients with advanced solid tumors harboring documented MAPK pathway alterations.

The age of patients eligible for inclusion in this study is ≥12 years to allow access to LTT462 treatment for adolescent patients with MAPK pathway alterations who have the same risk/benefit as the adult population. [redacted] The inclusion of patients ≥12 years is supported by published literature showing that adolescents have similar toxicity profiles, maximum tolerated doses, and pharmacokinetic parameters compared to adults.

The statistical analysis of the primary endpoints other than incidence of dose limiting toxicities (DLTs) during the dose escalation part [redacted] will be descriptive (Section 10.4.2.1). No hypotheses or models will be considered. Incidence of DLTs during the dose escalation part will be analyzed using an adaptive Bayesian model. Sample size requirements are provided in Section 10.8.

Dose Escalation Part

All patients enrolled during the dose escalation part of the study, will receive LTT462 in order to evaluate its safety and tolerability. On C1D1 only 1 dose will be given (in the morning) for all regimens. The evening dose on C1D1 will be omitted for the BID regimen. In addition, dosing will be omitted on the second day of the first cycle (C1D2; a cycle is defined as 28 days) for all regimens. This is to allow for a 48 hour sampling to fully characterize LTT462 PK parameters, such as total plasma exposures (AUC_{inf}) and T½, and PD.

The dose escalation for the QD [redacted] regimens will be guided by a Bayesian hierarchical logistic regression model (BHLRM) based on the first cycle DLT data of the study treatment. This model estimates the relationship between dose and the probability of a patient experiencing a DLT in the different cohorts investigated in the escalation part, following different regimens [redacted]. The model has the flexibility to allow for the case in which the dose-toxicity relationship is similar for some strata and the case in which the relationship is different for one or more strata. In the event that the relationship is similar, then the model structure will allow borrowing of information between those strata identified as exchangeable, which will in turn lead to improved estimation of the dose-toxicity relationship. The BHLRM is a hierarchical adaptation of the Bayesian logistic regression model (BLRM), a well-established method to estimate the MTD and/or RDE in cancer patients.

If, in addition, [redacted] BID regimen are explored, dose escalation decisions will be guided by a separate BLRM. Both Bayesian models, BHLRM and BLRM, will be guided by the escalation with overdose control (EWOC) principle to control the risk of DLT in future patients. The use of Bayesian response adaptive models for small datasets has been accepted by European Medicines Agency (Guideline on clinical trials in small populations, 2007) and endorsed by numerous publications (Babb et al 1998, Neuenschwander et al 2008), and its development and appropriate use is one aspect of the FDA's Critical Path Initiative.

The dose(s) identified by the model as satisfying the EWOC criterion at any given time point in the trial will be based on the entire history of all DLT information from previous cohorts up to that point. The model then provides information on the risk of DLT at all doses for future patients.

The decisions on new dose levels and regimens are made jointly by the Investigators and Novartis study personnel and will be based on patient tolerability and safety evaluations (for doses satisfying EWOC under the respective Bayesian model) and guided by PK, PD, and preliminary anti-tumor activity information available at the time of the decision making (Section 6.2.3).

[redacted]

2.3 Rationale for dose and regimen selection

In this study the selection of dose and regimen of LTT462 is based on the currently available non-clinical information (Section 1.2.2).

The starting dose of LTT462 in the dose escalation part of the FIH trial is 45 mg QD. [redacted]

Provisional doses for dose escalation can be found in Table 6-2.

In the dose expansion part, patients will be treated with LTT462 monotherapy at the recommended dose and regimen selected, which will be based on the dose escalation data. [redacted]

Initially the clinical regimen for this FIH study with LTT462 will be a continuous once daily dosing schedule. A QD regimen was demonstrated to be efficacious and tolerated in preclinical studies (Section 1.2.2.1). [redacted]

Depending on clinical experience with the starting regimen of QD dosing (in case emerging PK, PD, and/or safety data indicate that QD regimen is not optimal), the Novartis Clinical Study team may decide to additionally explore BID [redacted] for newly enrolled patients during the dose escalation part. [redacted] BID [redacted] regimens are supported by preclinical findings, where efficacy was achieved with either QD, BID [redacted] regimens. [redacted]

[redacted]

3 Objectives and endpoints

Objectives and related endpoints are described in Table 3-1 below.

Table 3-1 Objectives and related endpoints

Objective	Endpoint	Analysis
Primary		Refer to Section 10.4
To characterize safety and tolerability of LTT462 and identify a recommended dose and regimen for future studies in adult and adolescent patients with advanced solid tumors harboring MAPK pathway alterations.	**Safety:** Incidence and severity of adverse events (AEs) and serious AEs (SAEs), including changes in laboratory values, vital signs, and ECGs. Incidence and nature of DLTs (dose escalation only) **Tolerability:** Dose interruptions, reductions, and dose intensity	
Secondary		Refer to Section 10.5
To evaluate the preliminary anti-tumor activity of LTT462	**For both parts:** Overall response rate (ORR), Disease Control Rate (DCR), Duration of Response (DOR), and Progression Free Survival (PFS) as per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 [redacted]	
To evaluate the pharmacokinetic (PK) profile of LTT462	Plasma concentrations and derived PK parameters of LTT462	
To assess the pharmacodynamic (PD) effect of LTT462	Changes from baseline of the PD marker DUSP6 in tumor tissue and in blood.	

4 Study design

4.1 Description of study design

This study is a Phase I, open-label, dose finding study with a dose escalation part and a dose expansion part in adult and adolescent patients with advanced solid tumors harboring documented MAPK pathway alterations. The study treatment will be taken until the patient experiences unacceptable toxicity, progressive disease and/or has treatment discontinued at the discretion of the Investigator or the patient, or due to withdrawal of consent.

[redacted]

4.1.1 Dose escalation

Initially all patients enrolled in the dose escalation part of the study will receive oral LTT462 QD in fasted condition, with the exception of C1D2, when the dose will be omitted to allow for 48h-PK and PD profile collection.

The safety (including the dose-DLT relationship) and tolerability of LTT462 will be assessed, and dose(s) and regimen(s) will be identified for use in the expansion part based on the review of this data. The RDE will also be guided by the available information on PK, PD, and preliminary anti-tumor activity [redacted]

If emerging PK, PD, safety data and/or preliminary anti-tumor activity indicate that the QD regimen is not optimal, the Novartis Clinical Study team may recommend an alternative dosing regimen (see Table 4-1) for newly enrolled patients during the dose escalation part. In which case the starting total daily dose identified at that time for these alternative regimens will satisfy the EWOC criterion as per the statistical model for the alternative regimen and will not be higher than the highest tested safe QD dose. This decision will be formally documented in the dose escalation meeting minutes, which will be distributed to all relevant parties. QD, BID [redacted] may be explored in parallel.

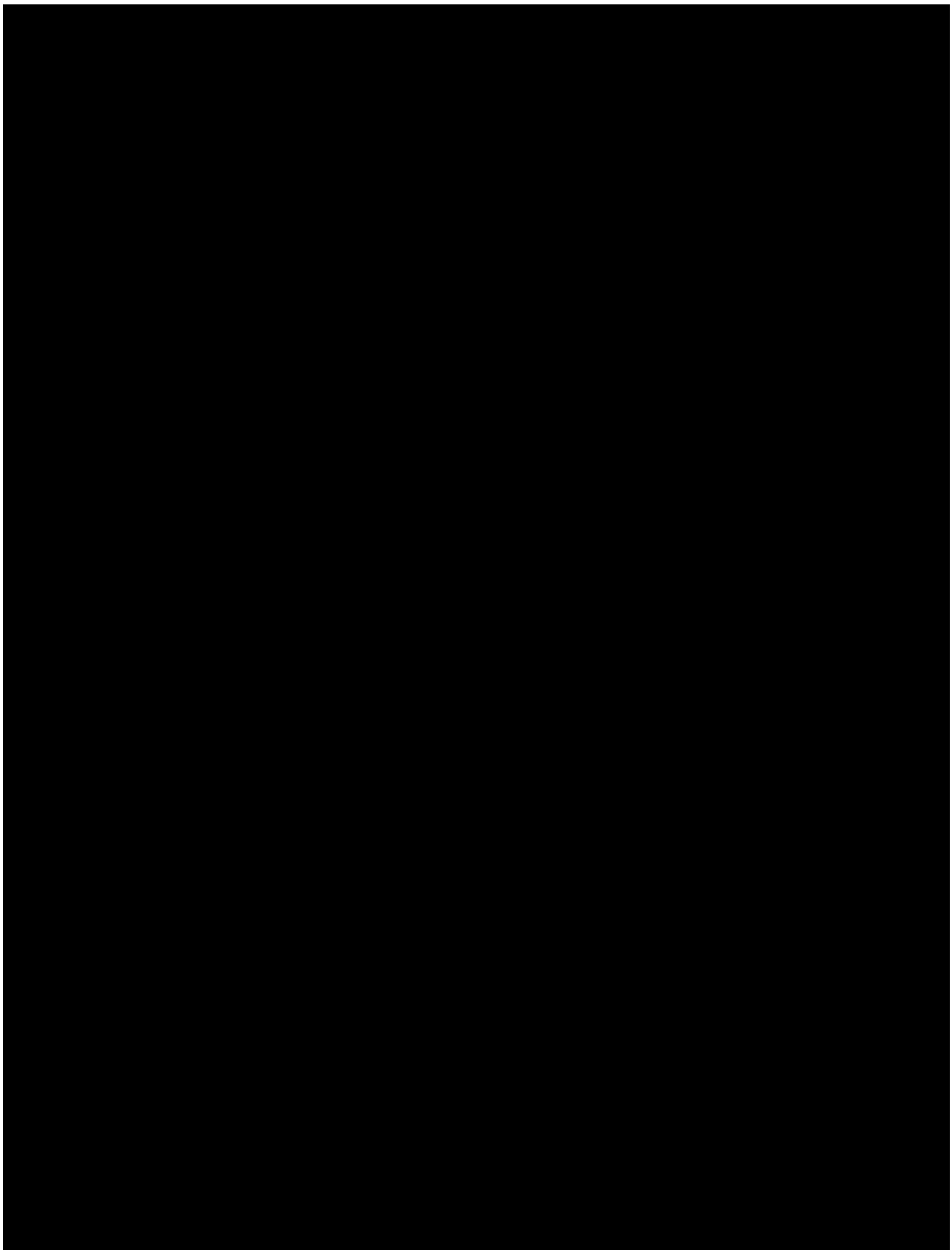
The dose escalation part plans to enroll at least 21 patients (Section 10.8.1) with advanced solid tumors harboring documented MAPK pathway alterations as listed in Table 5-1, with at least six patients treated at dose and regimen selected for dose expansion part (MTD or lower dose) (Section 6.2.3). Testing of additional regimens e.g. BID dosing in the dose escalation may increase patient numbers above those stated. Once RDE(s) has/have been identified, the dose expansion will be opened to patient enrollment.

[redacted]

Table 4-1 LTT462 regimens

Starting Regimen	Provisional [redacted]	Other Regimens
QD	[redacted]	
	BID (dosing two times a day for a 4 week cycle)	

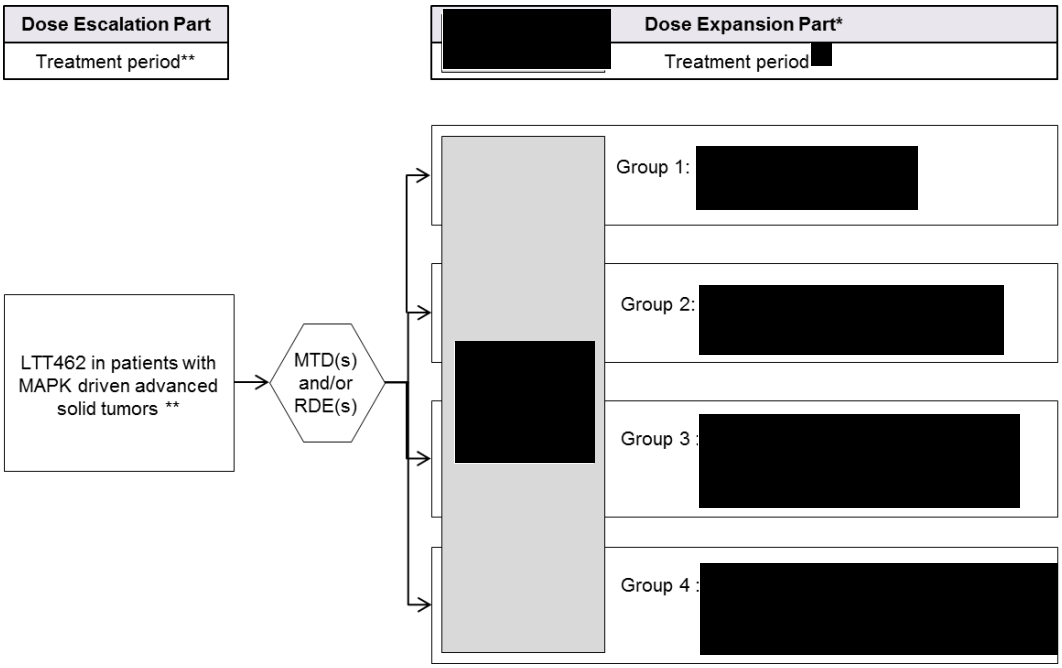
[redacted]



[redacted]

Figure 4-1 Study design

Dose Escalation and Dose Expansion



* More than one dose level and /or regimen, in [redacted], may be investigated

** No dosing on C1D2 to allow for 48h-PK and PD profile collection. Additionally the evening dose on C1D1 will be omitted for the BID regimen.

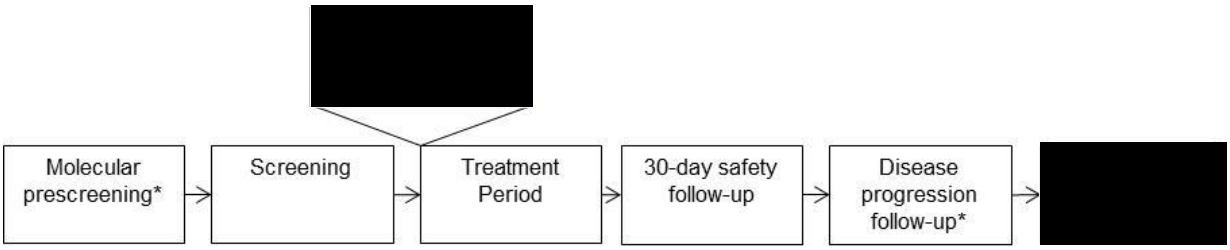
[redacted]

Study visit flow

Patients will undergo clinical and laboratory assessments during screening/baseline and periodically during treatment as outlined in Table 7-1.

For study visit flow detailed information is provided in Section 7.1.

Figure 4-2 Study visit flow



*as applicable

4.2 Timing of interim analyses and design adaptations

No formal interim analyses are planned for the study. However, the dose-escalation design foresees that decisions based on the current data are taken before the end of the study (Section 6.2.3). Adult and adolescent patients will be analyzed together as one population.

During the dose expansion phase, cumulative study data (including safety, tolerability, preliminary anti-tumor activity, PK, and PD) will be reviewed on an ongoing basis by Novartis and study investigators.

4.3 Definition of end of the study

The study will end when the treatment period and 30-day safety follow-up have been completed for all patients, when survival follow-up (for expansion patients only) has additionally has been completed, as described in Section 7.1.7, or when the study is terminated early.

Refer to Section 10 for details of timing of the primary analysis and final reporting of data.

4.4 Early study termination

The study can be terminated at any time for any reason by Novartis. Should this be necessary, the patient(s) should be seen as soon as possible for an end of treatment (EoT) visit and the same assessments for EoT, as described in Section 7.1.5 for a patient who discontinued treatment or a withdrawn patient, should be performed. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the patient's interests. The investigator will be responsible for informing

Institutional Review Boards (IRBs) and/or Ethics Committees of the early termination of the trial.

5 Population

5.1 Patient population

In this study, LTT462 will be administered to adult and adolescent (≥12 years old) patients with advanced solid tumors harboring MAPK alteration(s) [redacted] Patients identified to have other molecular alterations in MAPK pathway may be eligible pending documented agreement between Novartis and Investigator.

[redacted]

The Investigator or designee must ensure that only patients who meet all the following inclusion and none of the exclusion criteria are offered treatment in the study. All data for the inclusion and exclusion criteria must be verifiable in the patient's source documents.

5.2 Inclusion criteria

Patients eligible for inclusion in this study have to meet **all** of the following criteria:

1. Able to understand and voluntarily sign the ICF and ability to comply with the study visit schedule and the other protocol requirements. Written informed consent must be obtained prior to any study specific procedures that are not part of standard of care. If consent cannot be expressed in writing, it must be formally documented and witnessed, ideally via an independent trusted witness.

   For adolescent patients: consent will be obtained from parent(s) or legal guardian(s) and the signature of at least 1 parent or guardian will be required. Investigators will also obtain assent of patients according to local, regional or national guidelines.

   For Japan only: written consent is necessary both from the patient and his/her legal representative if he/she is under the age of 20 years.
2. Patient (male or female) ≥ 12 years of age

3. All patients participating in this clinical trial must have progressed following standard therapy, or for whom, in the opinion of the Investigator, no effective standard therapy exists, is tolerated or appropriate.
4. ECOG (Eastern Cooperative Oncology Group) performance status ≤ 1
5. Presence of at least one measurable lesion according to RECIST v1.1 (Appendix 1).

[redacted]

Dose escalation part:

Patients must have advanced solid tumors harboring at least one of the MAPK pathway alterations listed in Table 5-1.

Dose expansion part:

[redacted] Group 1:
Group 2:
Group 3:

[redacted]

[redacted] Group 4:

[redacted]

Note: Enrollment of patients with MAPK alteration(s) other than listed in Table 5-1 may be possible (dose expansion and dose escalation), but only after documented agreement between Novartis and the Investigator. [redacted]

7. Patients must have a site of disease amenable to biopsy and be a candidate for tumor biopsy according to treating institution's guidelines. Patients must be willing to undergo a new tumor biopsy [redacted].

   For adolescent patients: new tumor biopsies [redacted] should be performed when feasible. However, exceptions may be granted after documented agreement between Novartis and the Investigator.

5.3 Exclusion criteria

Patients eligible for this study must not meet **any** of the following criteria:

1. Prior treatment with ERK inhibitors.

[redacted]

4. History or current evidence of retinal vein occlusion (RVO) or current risk factors for RVO [redacted]

[redacted]

- Any medical condition that would, in the investigator's judgment, prevent the patient's participation in the clinical study due to safety concerns or compliance with clinical study procedures. [redacted]
- Patients with malignant disease, other than that being treated in this study. [redacted]

[redacted]

10. Patients receiving proton pump inhibitors (PPI) which cannot be discontinued 3 days prior to the start study treatment and for the duration of the study (Appendix 2).

[redacted] Clinically significant cardiac disease [redacted]

[redacted]

6 Treatment

6.1 Study treatment

The investigational drug to be used as the study treatment in this study is LTT462.

6.1.1 Dosing regimen

Table 6-1 Dose and treatment schedule

Study treatments	Pharmaceutical form and route of administration	Dose	Frequency and/or Regimen*
LTT462	Capsule for oral use	As assigned	Daily **

* If emerging PK and/or safety data indicate that this regimen is not optimal, the Novartis Clinical Study team may recommend an alternative dosing regimen in the treatment period for newly enrolled patients such as [redacted], BID [redacted] (Section 4.1).

** Study treatment will be omitted on C1D2 of the treatment period for all dosing regimens, see Section 4.1 or Table 7-1. Additionally the C1D1 evening dose will be omitted for BID dosing.

LTT462 should be taken as follows:

- LTT462 will be administered orally at flat-fixed doses (not by body weight or body surface area).
- Adolescent patients will be treated with the same dose as adult patients (see Section 2.3).
- Patients should take their dose at approximately the same time [redacted] on each day of dosing with a glass of water [redacted]
- Study treatment should be taken in the morning (for BID dosing, the study treatment should be taken in the morning and in the evening. [redacted]
- The C1D2 should be omitted for all dosing regimens. Additionally the C1D1 evening dose should be omitted for the BID regimen.
- On the days of PK sampling, the patients should take their doses in the clinic where the administration of LTT462 will be supervised and administration time recorded.
- The capsules should be ingested whole and should not be chewed or crushed.
- If multiple capsules are required for a dosage, then all capsules for that dose should be ingested in a short period of time as possible (i.e., not slower than 1 capsule every 2 minutes).

[redacted]

- If vomiting occurs following the dosing of study treatment, re-dosing is not permitted and dosing should resume at the next scheduled dose. If the vomiting occurs on full PK sampling days within the first 4 hours post-dosing, this event should to be recorded on the dose administration PK electronic Case Report Form (eCRF) page, as well as on the adverse event page, as appropriate.
- If the patient forgets to take the scheduled dose and more than 4 hours has passed since the scheduled time of study treatment intake, that dose should be skipped and treatment should continue with the next scheduled dose at the prescribed level (missed doses should not be replaced or made up at the next scheduled dosing).
- All dosages prescribed and dispensed to the patient and all dose changes during the study must be recorded on the Dosage Administration Record eCRF.

The investigator or responsible site personnel should instruct the patient to take the study drug exactly as prescribed to promote compliance.

Patients should inform the investigational site staff of any missed or delayed doses.

6.1.2 Treatment duration

Patients may be discontinued from study treatment earlier due to unacceptable toxicity, progressive disease, if treatment is discontinued at the discretion of the investigator or the patient and/or the patient withdraws consent. Refer to Section 7.1.3 and Section 7.1.4.

6.2 Dose escalation guidelines

6.2.1 Starting dose rationale

The selection of the starting dose follows the ICH S9 guidelines for choosing a starting dose for a FIH trial conducted in patients with cancer.

6.2.2 Provisional dose levels

Table 6-2 describes the starting dose and the dose levels that may be evaluated during the study.

Table 6-2 Provisional dose levels

Dose level	Proposed daily dose*	Increment from previous dose
-1**	30 mg	-33%
1	45 mg	(starting dose)
2	100 mg	122%
3	200 mg	100%
4	300 mg	50%
5	400 mg	33%
6	500 mg	25%
7	600 mg	20%

*It is possible for additional and/or intermediate dose levels to be added during the course of the study. Cohorts may be added at any dose level below the MTD in order to better understand safety, PK or PD.
**Dose level -1 represents treatment doses for patients requiring a dose reduction from the starting dose level. No dose reduction below dose level -1 is permitted for this study.

Dose escalation will continue until a recommended dose (MTD(s) or lower dose(s)) and regimen is determined. At all decision time points, the adaptive Bayesian models permits alterations in the dose increments based on the observed DLTs. Multiple cohorts may be opened simultaneously in order to study more than one dose or dose regimen in order to better understand safety, PK and or PD, as long as selected dose levels satisfy the EWOC criterion and satisfy the rules for escalation described in Section 6.2.3 (e.g., at most 100% increase from previous dose, with the exception of the first dose escalation for which an increase of up to 122% will be considered. [redacted]

6.2.3 Guidelines for dose escalation and determination of MTD(s)/RDE(s)

6.2.3.1 MTD definition

The MTD is defined as the highest drug dosage not expected to cause DLT in 33% or more of the treated patients in the first cycle of LTT462 treatment during the escalation part of the study. AEs and laboratory abnormalities considered to be DLTs are defined in Table 6-3. If different dose regimens are tested in addition to QD (such as BID, [redacted] a different dose for each regimen may correspond to this definition.

The recommended dose(s) selected for study in the dose expansion part will be identified based on the review of all study data, including the estimated MTD if achieved. The recommended dose(s) will not exceed the MTD but may be a lower dose if supported by the review of safety, PK, PD and preliminary anti-tumor activity at all doses.

6.2.3.2 Dose cohort modification

For the purposes of dose escalation decisions, each cohort will consist of 1 to 6 newly enrolled patients who will be treated at the specified dose level. The first cohort will be treated with the starting dose of 45 mg QD.

Patients must complete a minimum of 1 cycle of treatment with the minimum safety evaluation and drug exposure or have had a DLT within the first cycle of treatment to be considered evaluable for dose escalation decisions (Section 10.1.4). Dose escalation decisions will occur when the cohort of patients has met these criteria.

If two patients (who may be in different cohorts) have experienced a toxicity of Common Terminology Criteria for Adverse events (CTCAE) grade 2, for which relationship to study drug cannot be ruled out; or when any single patient experiences a DLT or adverse event (AE) of CTCAE grade 3 or greater during Cycle 1, the cohort size will be increased to between 3 and 6 evaluable patients for the current and subsequent cohorts.

If a minimum of 3 patients are required in a cohort and only 2 of these patients are evaluable and neither subject has experienced a treatment-related toxicity > CTCAE grade 1, dose escalation decisions may be considered.

Dose escalation decisions will be made by the Investigators and Novartis study personnel. Decisions will be based on a synthesis of all relevant data available from all dose levels evaluated in the ongoing study including safety information, DLTs, all CTCAE Grade ≥ 2 toxicity data during Cycle 1, PK, and PD data from evaluable patients. The recommended dose for the next cohort of subjects will be guided by the BHLRM subject to the EWOC principle (Section 10.4.2).

The adaptive Bayesian methodology provides an estimate of all dose levels of LTT462 that do not exceed the MTD for each regimen and incorporates all DLT information at all dose levels for this estimation. In general, the next dose will have the highest chance that the DLT rate will fall in the target interval (16-33%) and will always satisfy the EWOC principle. The dose for the next cohort will not exceed a 100% increase from the previous dose, with the exception of the first dose escalation in which increases of up to 122% will be considered (see Section 6.2.2). Smaller increases in dose may be recommended by the Investigators and Novartis upon consideration of all of the available clinical data. Any dose escalation decision made by Investigators and Novartis personnel will not exceed the dose level permissible following the application of the EWOC principle to inference from the Bayesian model. If needed to better define the dose-toxicity relationship additional patients may be enrolled to the current dose level, to a preceding dose level, or to an intermediate dose level before proceeding with further dose escalation.

If 2 patients in a previously untested dose level experience a DLT, further enrollment to that cohort will stop and the Bayesian model will be updated with this new information. The next cohort will be opened at the next lower dose level or an intermediate dose level (see Table 6-2 and Appendix 5) that satisfies the EWOC criteria. However, if 2 patients in a new cohort at a previously tested dose level experience a DLT (e.g., a total of 8 patients are treated on this dose level with 2 DLTs observed), further enrollment to that cohort will stop, the Bayesian model will be updated with this new information and re-evaluation of the available safety, PK, and PD data will occur. By incorporating information gained at the preceding dose cohorts, additional patients may be enrolled into the current dose level or a lower dose level as agreed by Investigators and Novartis personnel and if the Bayesian model predicts that the risk for this dose to exceed the MTD(s) remains below 25% (EWOC). Re-escalation may then occur if data

in subsequent cohorts supports this EWOC criteria are satisfied and Investigators and Novartis personnel agree.

To better understand the safety, tolerability, and PK of LTT462 additional cohorts of patients may be enrolled at preceding dose levels, or to intermediate dose levels, before or while proceeding with further dose escalation.

If a decision is made to escalate to a higher dose level but one or more additional patient(s) treated at the preceding dose level experiences a DLT during the first cycle of treatment, then the Bayesian model will be updated with this new information before any additional patients are enrolled at that higher dose level. Patients ongoing will continue treatment at their assigned dose levels.

Dose escalation will continue until identification of the MTD(s) or until Novartis and Investigators reach a consensus that based on the clinical data, a suitable lower dose is recommended for use in the expansion part for one or more of the dose and regimen (schedule [redacted]). This will occur when the following conditions are met:

1. at least 6 patients have been treated with this dose, schedule, [redacted]
2. this dose satisfies one of the following conditions:
   a. the posterior probability of targeted toxicity at this dose exceeds 50% and is the highest among potential doses.
   b. a minimum of 21 patients have already been treated on the trial.
   c. significant activity is seen early in the dose escalation part, in which case a recommended dose/regimen may be identified and the dose expansion part may be initiated without determination of the MTD.
3. it is the dose recommended for patients, either per the model or by review of all clinical data by Novartis and Investigators in a dose-escalation teleconference, see Section 6.2.3.1.

6.2.3.3 Implementation of Dose Escalation Decisions

To implement dose escalation decisions, the available toxicity information (including AEs and laboratory abnormalities that are not DLTs), the recommendations from the Bayesian model after all patients in the cohort are assessed as evaluable, and the available PK and PD information will all be evaluated by the Investigators and Novartis study personnel (including the study physician and statistician) during a dose decision meeting by teleconference. Drug administration at the next higher dose level may not proceed until the investigator receives written confirmation from Novartis indicating that the results of the previous dose level were evaluated and that it is permissible to proceed to a higher dose level.

6.2.3.4 Intra-Patient dose escalation

Intra-patient dose escalation is not permitted at any time within the first 4 cycles of treatment. After the 4th cycle is completed, individual patients may be considered for treatment at a dose of LTT462 higher than the dose to which they were initially assigned. In order for a patient to be treated at a higher dose of LTT462, he or she must have tolerated the lower dose for at least 4 cycles of therapy (i.e. he or she must not have experienced any LTT462-related toxicity CTCAE grade ≥ 2 at the lower dose originally assigned). Moreover, the new, higher dose with which the patient is to be treated must be a dose that has completed evaluation and has not exceeded the MTD estimated by the Bayesian model given all available data.

There is no limit to the number of times a patient may have his or her dose of LTT462 increased. Further increase after the initial intra-patient dose escalation will be subject to the same rule as for the initial intra-patient dose escalation. Consultation and agreement with Novartis must occur prior to any intra-patient dose escalation occurring. These changes must be recorded on the Dosage Administration Record eCRF.

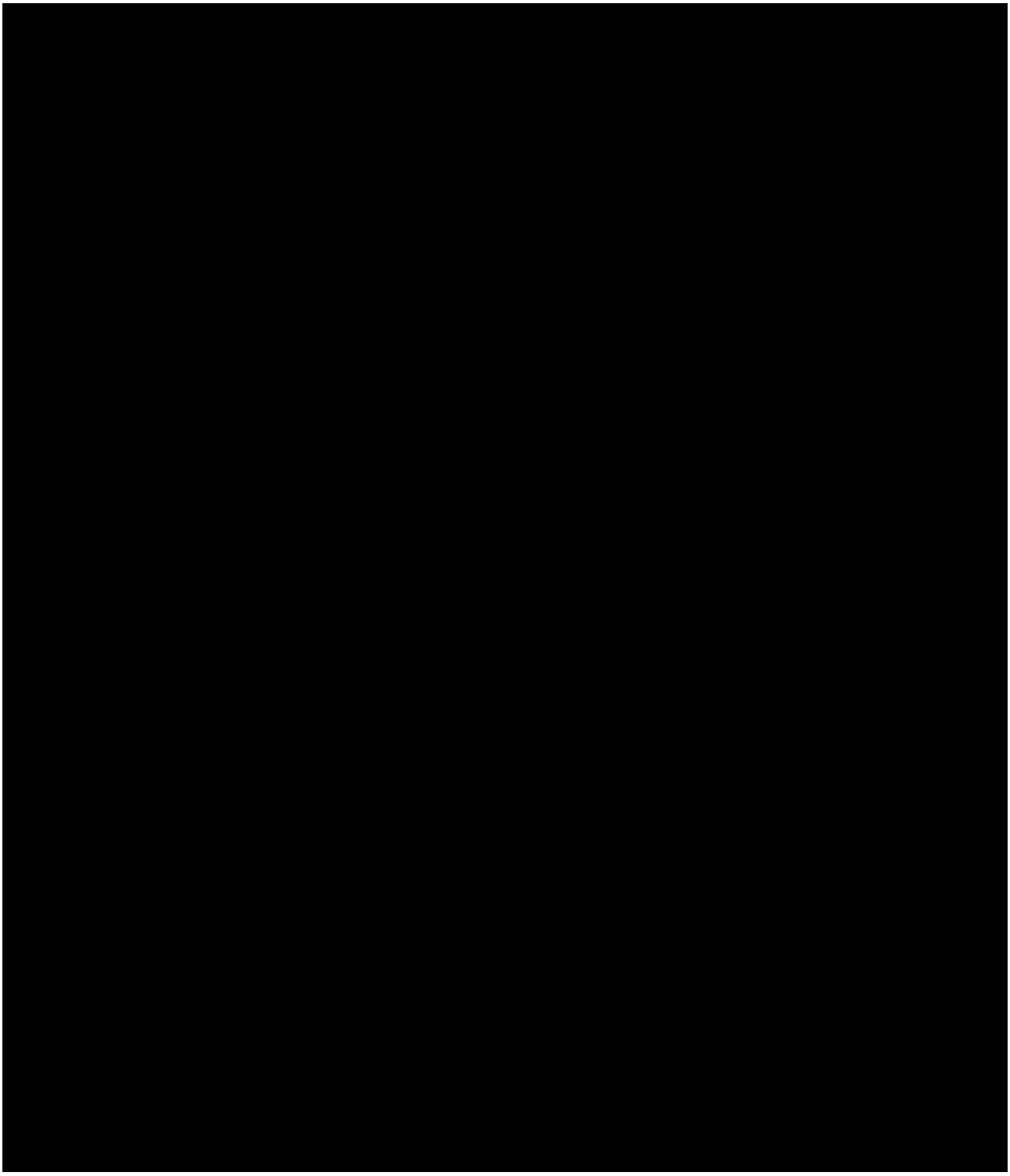
Data from the first cycle of treatment at the new dose level will not be formally included into the statistical model describing the relationship between dose and occurrence of DLT. However, this data will be incorporated into the clinical assessment of safety within a dose escalation teleconference.

With the exception of ophthalmological assessments (see Section 7.2.2.7), patients will continue with the visit schedule in line with the duration of their treatment (i.e. they would not have to restart at C1D1 assessments but continue from C5D1 if they).

6.2.4 Definitions of dose limiting toxicities (DLTs)

A dose-limiting toxicity (DLT) is defined as an AE or abnormal laboratory value where the relationship to LTT462 cannot be ruled out, and is assessed as not primarily related to disease, disease progression, inter-current illness, or concomitant medications that occurs within the first 28 days of treatment with LTT462 and meets any of the criteria [redacted] National Cancer Institute (NCI) CTCAE version 4.03 will be used for all grading.

The investigator must notify the Sponsor immediately of any unexpected CTCAE grade ≥ 3 AEs or laboratory abnormalities. Prior to enrolling patients into a higher dose level, CTCAE grade ≥ 2 AEs will be reviewed for all patients at the current dose level.



6.3 Dose modifications

6.3.1 Dose modification and dose delay

For patients who do not tolerate the protocol-specified dosing schedule due to DLT(s), dose adjustments are permitted in order to allow the patient to continue the study treatment. For the

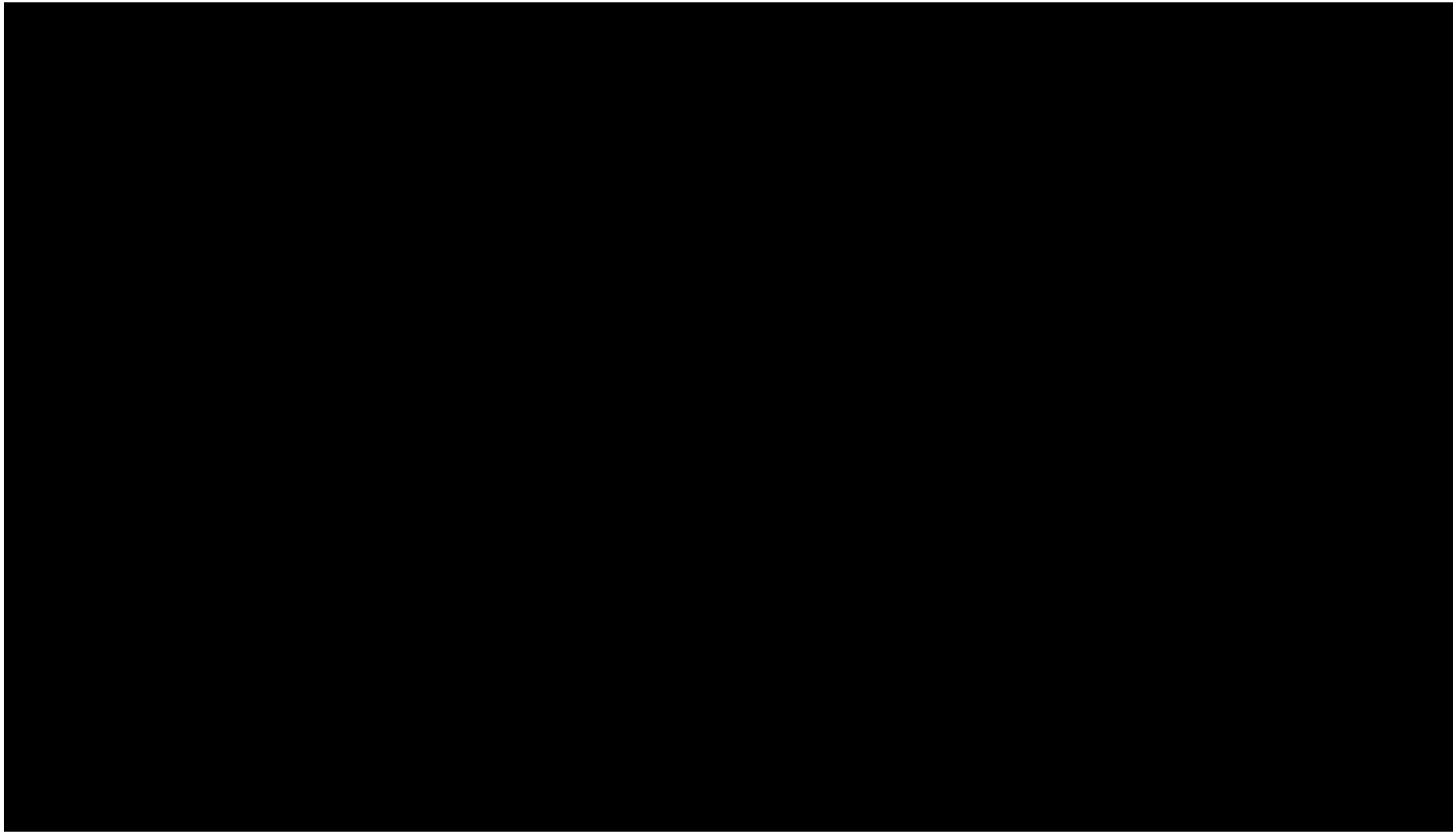
dose escalation part of the study, dose reductions during Cycle 1 are only allowed if a DLT is observed and recorded.

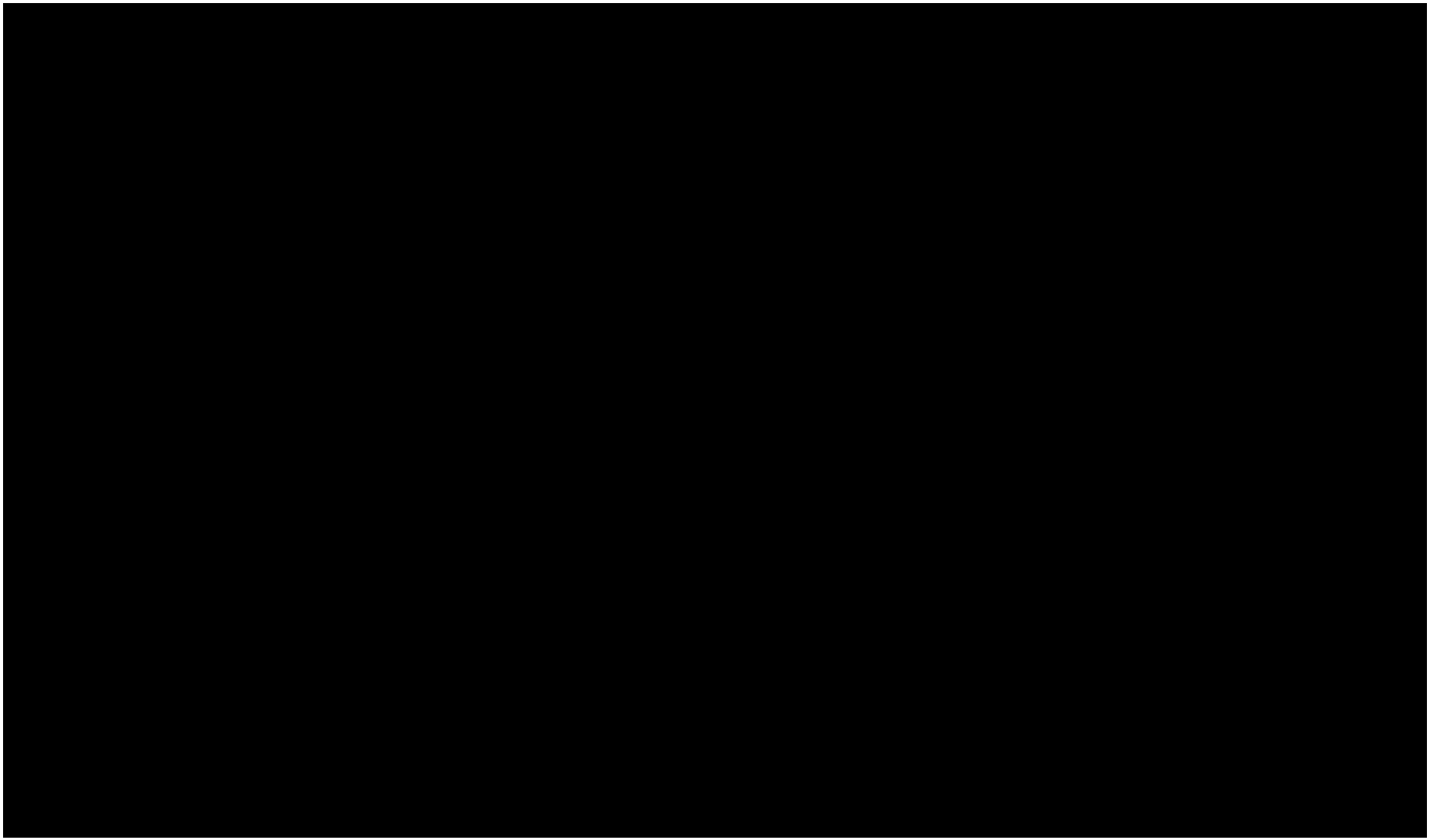
The following guidelines need to be considered:

- The criteria for dose modifications and dose interruptions (i.e., interruption and re-initiation criteria for LTT462 treatment) for toxicities considered at least possibly related to the study treatment are outlined in Table 6-4. All dose modifications should be based on the worst preceding toxicity (CTCAE version 4.03).
- A patient must discontinue treatment with LTT462 if, after treatment is resumed at a lower dose, the toxicity recurs with the same or worse severity, unless in the opinion of the investigator it is in the patient's best interest to continue LTT462, and upon documented agreement with Novartis.
- For each patient, once a dose level reduction has occurred, the dose level may not be re-escalated during subsequent treatment cycles with LTT462.
- If, due to study drug related toxicity, a patient requires a dose interruption of > 21 days from the intended day of the next scheduled dose, then the patient should be discontinued from the study treatment. However, if the patient with a dose interruption of > 21 days is clearly benefiting from the study treatment and in the opinion of the investigator it is in the patient's best interest to continue LTT462, upon documented agreement with Novartis, the patient may remain on study treatment. This decision must be available in the source documentation and described as an investigator comment in the eCRF.

In case of study treatment interruption, visit schedule should still be followed and assessments performed as per Table 7-1.

Any dose modification and dose delay must be recorded on the Dosage Administration Record eCRF.





6.3.2 Follow-up for toxicities

Patients whose treatment is interrupted or permanently discontinued due to an adverse event or clinically significant laboratory value, must be followed up at least once a week (or more frequently if required by institutional practices, or if clinically indicated) for 4 weeks, and subsequently at approximately 4 week intervals, until resolution or stabilization of the event, whichever comes first. Appropriate clinical experts such as ophthalmologist, endocrinologist, dermatologist, psychiatrists etc. should be consulted as deemed necessary.

All patients must be followed up for adverse events and serious adverse events for 30 days following the last dose of LTT462

6.3.3 Anticipated risks and safety concerns of the study drug

Appropriate eligibility criteria and specific DLT definitions, as well as specific dose modification and stopping rules are included in this protocol. Recommended guidelines for prophylactic or supportive treatment for expected toxicities, including management of study drug induced adverse events will be as per institutional guidelines. Refer to preclinical toxicity (Section 1.2.2.4) and/or the [LTT462 Investigator's Brochure].

6.4 Concomitant medications

The patient must be told to notify the investigational site about any new medications he/she takes after the start of the study drug. All medications (other than study drug) and significant non-drug therapies (including physical therapy, herbal/natural medications and blood transfusions) administered during the study must be listed on the Prior and Concomitant Medications or the Surgical and Medical procedures eCRF.

6.4.1 Permitted concomitant therapy

In general, the use of any concomitant medication/therapy, including over-the-counter medications deemed necessary for the care of the patient or to treat AEs is permitted during the study except for those specified as prohibited in Section 6.4.3.

6.4.2 Permitted concomitant therapy requiring caution and/or action

Permitted therapy to be used with caution in this study includes:

[redacted]

- Agents that modify gastric pH: If antacids and/or H2 receptor antagonists are indicated, follow guideline provided in Appendix 2 regarding timing of administration of these agents relative to LTT462 dosing.

If any of the above drugs cannot be avoided, caution should be used during concomitant administration with LTT462. The patient and the Investigator should be aware of potential signs of overdose of the concomitant medication and in the event of suspected toxicity; administration of either the substrate or LTT462 should be discontinued according to Investigator judgment.

Refer to (Appendix 2) for a list of medications that are to be used with caution.

6.4.3 Prohibited concomitant therapy

[redacted] In addition, the following classes of medications or herbs are prohibited:

[redacted]

- PPIs are prohibited.

[redacted]

- Refer to Appendix 2 for a list of medications that are prohibited.

6.5 Patient numbering and treatment assignment

6.5.1 Patient numbering

Each patient is identified in the study by a Subject Number (Subject No.), that is assigned when the patient is first enrolled for pre-screening (if applicable) or when they are enrolled for screening. The subject number is retained as the primary identifier for the patient throughout his/her entire participation in the trial. The Subject No. consists of the Center Number (Center No.) (as assigned by Novartis to the investigative site) and a sequential patient number suffixed to it, so that each subject is numbered uniquely across the entire database. Upon signing the informed consent form, the patient is assigned to the next sequential Subject No. available to the investigator [redacted].

Patients who do not meet all of the inclusion or exclusion criteria may potentially be re-screened for consideration in the trial. If a patient is re-screened, the same Subject No. should be used.

6.5.2 Treatment assignment

This is a non-randomized trial. The assignment of a patient to a particular cohort or group will be coordinated by the sponsor.

6.6 Study treatment preparation and dispensation

The investigator or responsible site personnel must instruct the patient or caregiver to take the study drugs as per protocol. Study drug(s), including instructions for administration, will be dispensed to the patient by authorized site personnel only, on an outpatient basis. Patients will be provided with adequate supply of study treatment for self-administration at home until at least their next scheduled study visit. [redacted] All dosages prescribed to the patient and all dose changes during the study must be recorded on the Dosage Administration Record eCRF.

6.6.1 Study treatment packaging and labeling

The study medication packaging has a 2-part label. Site personnel will add the patient number on the label. Immediately before dispensing the package to the patient, site personnel will detach the outer part of the label from the packaging and affix it to the source document (Drug Label Form) for that patient's unique patient number.

Study treatment labels will be in the local language and comply with the legal requirements of each country. They will include storage conditions for the drug.

Study treatment will be packed under the responsibility of the Novartis Drug Supply Management department and will be supplied as open label supply which allows the patient to take medication at home.

[redacted]

6.6.2 Drug supply and storage

Study treatments must be received by designated personnel at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designated site personnel have access. Upon receipt, the study treatment should be stored according to the instructions specified on the drug labels and in the LTT462 Investigator's Brochure.

Table 6-5 Supply and storage of study treatments

Study treatments	Supply	Storage
LTT462	Centrally supplied by Novartis	Refer to study treatment label

6.6.3 Study drug compliance and accountability

6.6.3.1 Study drug compliance

Compliance will be assessed by the investigator and/or study personnel at each patient visit and information provided by the patient and/or caregiver will be captured in the Drug Accountability Form. This information must be captured in the source document at each patient visit.

6.6.3.2 Study drug accountability

The investigator or designee must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. Drug accountability will be noted by the field monitor during site visits and at the completion of the study. Patients will be asked to return all unused study treatment and packaging on a regular basis, at the end of the study or at the time of study treatment discontinuation.

At study close-out, and, as appropriate during the course of the study, the investigator will return all used and unused study treatment, packaging, drug labels, and a copy of the completed drug accountability log to the Novartis monitor or to the Novartis address provided in the investigator folder at each site.

6.6.4 Disposal and destruction

The study drug supply can be destroyed at the local Novartis facility, Drug Supply group or third party, as appropriate.

Study drugs destruction at the investigational site will only take place if permitted by local regulations and authorized by Novartis in a prior agreement.

7 Visit schedule and assessments

7.1 Study flow and visit schedule

Table 7-1 lists all of the assessments and indicates with an "X" the visits at which they are performed.

All data obtained from these assessments must be supported in the patient's source documentation. The "Category" column of the table indicates which assessments produce data to be entered into the clinical database (D) and those which will remain in source documents only (S).

No case report form (CRF) will be used as a source document.

For Japan only, patients are required to be hospitalized in Cycle 1 of the dose escalation part.

Visits and schedule windows

During the course of the study visits, test and/or procedures should occur on schedule whenever possible.

- Screening evaluations must be performed ≤ 14 days prior to first dose of study treatment (≤ 28 days for baseline radiological assessments).
- Laboratory assessments performed as part of the screening evaluations that are within 72 hours of the first dose of study treatment, are not required to be repeated on the first dosing day. [redacted]
- Full PK sampling should be performed on the specified day of dosing and time point (see Table 7-6 and Table 7-7 for sample windows).
- For imaging assessments, a ±7 day window is allowed; however, confirmatory scan must be performed at least 4 weeks after the initial scan indicating response.

In any case, if the dosing schedule is changed, the visit evaluation schedule will follow Table 7-1 without changes.

Table 7-1 Visit evaluation schedule

		Protocol Section	Screening Period		[redacted]	Treatment Period															End of study treatment (EoT)	Follow-up period		[redacted]
Visit Name	**Category**		**Molecular Pre-screening**	**Screening**		**Cycle 1**								**Cycle 2**				**Cycle 3 to Cycle 6**		**Subsequent cycles**		**30 days safety follow-up**	**Disease progression F/U**	
Day of cycle				**-14 to -1**		**1**	**2**	**3**	**8**	**15**	**16**	**17**	**22**	**1**	**8**	**15**	**22**	**1**	**15**	**1**				
Informed Consent																								
Obtain Molecular Pre-Screening Informed Consent	D	7.1.1	X[a]																					
Obtain informed consent	D	7.1.2		X																				
Patient history																								
Demography	D	7.1.2.2	X																					
Inclusion/exclusion criteria	D	5		X																				
Medical History	D	7.1.2.2		X																				
Diagnosis and extent of cancer	D	7.1.2.2		X																				
Smoking history	D	7.1.2.2		X																				

		Protocol Section	Screening Period		Treatment Period																Follow-up period		
Visit Name	**Category**		**Molecular Pre-screening**	**Screening**	**Cycle 1**								**Cycle 2**				**Cycle 3 to Cycle 6**		**Subsequent cycles**	**End of study treatment (EoT)**	**30 days safety follow-up**	**Disease progression F/U**	
Day of cycle				**-14 to -1**	**1**	**2**	**3**	**8**	**15**	**16**	**17**	**22**	**1**	**8**	**15**	**22**	**1**	**15**	**1**				
Prior antineoplastic therapy	D	7.1.2.2		X																			
Prior/concomitant medications	D	7.1.2.2		X																			
Tumor progression status at study enrollment	D	7.1.2.2		X																			
Efficacy Assessments																							
Tumor evaluation	D	7.2.1		X													C3, C5		C7[b]	X		X	
Safety Assessments																							
Physical examination	S	7.2.2.1		X	X								X				X		X	X			
Vital signs	D	7.2.2.2		X	X	X	X	X	X	X	X[c]	X	X	X	X	X	X	X	X	X			
Height	D	7.2.2.3		X																			

		Protocol Section	Screening Period		[redacted]	Treatment Period															End of study treatment (EoT)	Follow-up period		[redacted]
Visit Name	**Category**		**Molecular Pre-screening**	**Screening**		**Cycle 1**								**Cycle 2**				**Cycle 3 to Cycle 6**		**Subsequent cycles**		**30 days safety follow-up**	**Disease progression F/U**	
Day of cycle				**-14 to -1**		**1**	**2**	**3**	**8**	**15**	**16**	**17**	**22**	**1**	**8**	**15**	**22**	**1**	**15**	**1**				
Weight	D	7.2.2.3		X		X								X				X		X	X			
Performance status	D	7.2.2.4		X		X								X				X		X	X			

		Protocol Section	Screening Period		[redacted]	Treatment Period															End of study treatment (EoT)	Follow-up period		[redacted]
Visit Name	**Category**		**Molecular Pre-screening**	**Screening**		**Cycle 1**								**Cycle 2**				**Cycle 3 to Cycle 6**		**Subsequent cycles**		**30 days safety follow-up**	**Disease progression F/U**	
Day of cycle				**-14 to -1**		**1**	**2**	**3**	**8**	**15**	**16**	**17**	**22**	**1**	**8**	**15**	**22**	**1**	**15**	**1**				
Laboratory evaluations																								
Hematology	D	7.2.2.5.1		X		X			X	X			X	X	X	X	X	X	X	X	X			
Chemistry	D	7.2.2.5.2		X		X			X	X			X	X	X	X	X	X	X	X	X			
Coagulation	D	7.2.2.5.3		X																	X			
Pregnancy test	D	7.2.2.5.4		X		X[d]								X				X		X	X	X		
Adverse events	D	8		X[e]		Continuously																		
Cardiac assessments		7.2.2.6																						
ECG	D	7.2.2.6.1																						
QD				X		X	X			X	X			X		X		X			X			
BID				X		X	X			X	X			X		X		X			X			
[redacted]																								
Cardiac imaging (MUGA or ECHO)	D	7.2.2.6.2		X										X							X			

		Protocol Section	Screening Period		Treatment Period															End of study treatment (EoT)	Follow-up period		
Visit Name	**Category**		**Molecular Pre-screening**	**Screening**	**Cycle 1**								**Cycle 2**				**Cycle 3 to Cycle 6**		**Subsequent cycles**		**30 days safety follow-up**	**Disease progression F/U**	
Day of cycle				**-14 to -1**	**1**	**2**	**3**	**8**	**15**	**16**	**17**	**22**	**1**	**8**	**15**	**22**	**1**	**15**	**1**				
[redacted]																							
PK sampling	D	7.2.3																					
QD					X	X	X	X	X	X			X		X		C3, C5			X			
BID					X	X	X	X	X	X			X		X		C3, C5			X			
[redacted]																							

		Protocol Section	Screening Period		[redacted]	Treatment Period															End of study treatment (EoT)	Follow-up period		[redacted]
Visit Name	**Category**		**Molecular Pre-screening**	**Screening**		**Cycle 1**								**Cycle 2**				**Cycle 3 to Cycle 6**		**Subsequent cycles**		**30 days safety follow-up**	**Disease progression F/U**	
Day of cycle				**-14 to -1**		**1**	**2**	**3**	**8**	**15**	**16**	**17**	**22**	**1**	**8**	**15**	**22**	**1**	**15**	**1**				
[redacted]																								
Biomarkers		7.2.4			[redacted]																			
Whole Blood for DUSP6	D	7.2.4.1.1				X	X	X		X	X	X[c]									X[f]		X[f]	
[redacted]																								

		Protocol Section	Screening Period		[redacted]	Treatment Period															End of study treatment (EoT)	Follow-up period			
Visit Name	**Category**		**Molecular Pre-screening**	**Screening**		**Cycle 1**								**Cycle 2**				**Cycle 3 to Cycle 6**		**Subsequent cycles**		**30 days safety follow-up**	**Disease progression F/U**	[redacted]
Day of cycle				**-14 to -1**		**1**	**2**	**3**	**8**	**15**	**16**	**17**	**22**	**1**	**8**	**15**	**22**	**1**	**15**	**1**				
Collection of archival paraffin blocks/slides or newly obtained tumor sample for molecular pre-screening (as applicable).	D	7.1.1 7.2.4	X																					
Collection of newly obtained tumor sample from biopsy/resection	D	7.2.4.1.1 7.2.4.3.1		X						[redacted]														
Study drug administration	D	6.1				X[h]		Continuously																
Antineoplastic therapies since discontinuation of study treatment	D	7.1.7.1																			X	X	X	X

		Protocol Section	Screening Period			Treatment Period														End of study treatment (EoT)	Follow-up period		
Visit Name	Category		Molecular Pre-screening	Screening		Cycle 1								Cycle 2				Cycle 3 to Cycle 6		Subsequent cycles		30 days safety follow-up	Disease progression F/U	
Day of cycle				-14 to -1		1	2	3	8	15	16	17	22	1	8	15	22	1	15	1				

7.1.1 Molecular pre-screening

All patients will be asked to sign a "molecular pre-screening informed consent" prior to the collection and analysis of an archival or newly obtained tumor sample to determine the molecular status of the tumor, unless existing local data can be used for inclusion in the study.

For inclusion in the dose escalation part, evidence of a MAPK pathway alteration may be obtained from existing local data for the patient or local testing of a tumor sample may be performed.

[redacted]

The results of existing local data must be captured on the appropriate eCRF upon enrollment onto the study after the patient has signed the main study ICF. Evidence of local data must be present in the source documentation.

7.1.2 Screening

When the patient is considered eligible for screening, the investigator should complete the Patient Registration Form and send it to Novartis. The allocation of patients to treatment cohorts and groups will be handled by the Novartis clinical study team.

A written ICF will be obtained from each patient before any study procedures not considered part of standard of care procedures are initiated.

The patients should be evaluated against the study inclusion and exclusion criteria of the study.

The clinical screening period starts once the MAPK pathway alteration(s) status of the patient is known, meets the eligibility requirements, and the patient has provided written ICF to participate in the study. Screening assessments have to be done within 14 days prior to the first dose of study treatment. Radiological tumor assessment by RECIST v1.1 (Appendix 1) should be conducted preferably within 7 days prior to the first dose of the study treatment; however tumor assessments up to 28 days prior to the first dose will be acceptable. The tumor assessment made during the screening period will provide the baseline tumor measurements, which will be used to determine future responses and/or progression. A complete list of screening evaluations is provided in the visit of assessments table (Table 7-1).

7.1.2.1 Information to be collected on screening failures

Patients who signed an Informed Consent Form but failed to be started on treatment for any reason will be considered a screen failure. Both subjects who signed a molecular pre-screening ICF but are considered ineligible after molecular pre-screening, as well as subjects who are found not eligible after signing the main study consent will be considered as screening failures, and data will be handled in the same manner.

The reason for molecular pre-screening failure or screening failure will be entered on the Screening Phase Disposition Page.

The demographic information, informed consent, and Inclusion/Exclusion pages must also be completed for Screen Failure patients. No other data will be entered into the clinical database for patients who are screen failures, unless the subject experienced a Serious Adverse Event during the Screening Phase (see Section 8 for serious adverse event (SAE) reporting details). For molecular pre-screening failures, only SAEs possibly related to a study procedure (i.e., tumor biopsy collection) will be reported.

7.1.2.2 Patient demographics and other baseline characteristics

Data will be collected on patient characteristics at baseline, including demographic information (age, gender, and race), smoking history and relevant medical history (history of disease and current disease status, staging, sites of disease, prior anticancer therapies, prior medication/ significant non-drug therapies) and any other assessments that are done for the purposes of determining eligibility for inclusion in the study.

Additionally, the rate at which the tumor was progressing at study enrollment (determined by comparing the sum of target lesions diameters of baseline scan to scan obtained prior to baseline – if available from patient's records) will be assessed to support [redacted] PK, PD, and/or preliminary anti-tumor activity based objectives.

All medications and significant non-drug therapies (including herbal medicines, physical therapy and blood transfusions) that are taken by the patient within the 4 weeks prior to their first dose of study drug must be recorded on the eCRF.

[redacted]

7.1.4 Treatment period

Treatment period is applicable for both dose escalation and dose expansion parts.

The treatment period will begin on the first day when patient receives LTT462. [redacted]

A treatment period cycle is defined as 28 days (4 calendar weeks) for the purposes of scheduling procedures and evaluations. Please refer to Table 7-1 for details of the timing of required assessments and Section 7.1 for visit windows.

Patients will be treated until the patient experiences progression of disease, development of unacceptable toxicity, withdrawal of informed consent, or death, whichever occurs first as described in Section 7.1.5 and Section 7.1.6.

Patients who have disease progression and have evidence of clinical benefit, such as disease shrinkage at other sites or symptomatic improvement, may continue treatment with LTT462. In addition, LTT462 treatment may be temporarily interrupted to permit local therapy for symptomatic metastases after disease progression has been documented. Patients who continue on treatment after disease progression should discontinue study treatment once they are no longer deriving benefit as assessed by the investigator. These decisions can only be taken upon documented agreement with the Novartis Medical monitor and a report of the discussions with Novartis must be recorded in the source documentation and in a comment in the eCRF.

7.1.5 Discontinuation of Study Treatment

Patients may voluntarily discontinue from the study treatment for any reason at any time. If a patient decides to discontinue from the study treatment, the investigator must make every effort (e.g. telephone, e-mail, letter) to determine the primary reason for this decision and record this information in the patient's chart and on the appropriate eCRF pages. They may be considered withdrawn if they state an intention to withdraw, fail to return for visits, or become lost to follow-up for any other reason.

The investigator should discontinue study treatment for a given patient if, he/she believes that continuation would be detrimental to the patient's well-being.

Study treatment may be discontinued under the following circumstances:

- Adverse Event
- Investigator's decision
- Progressive disease
- Lost to follow-up
- Technical problems
- Study terminated by Novartis
- Patient/guardian decision
- Study treatment interruption of > 21 consecutive days; unless the investigator feels there is clinical benefit
- Protocol deviations

Study treatment must be discontinued under the following circumstances:

- Pregnancy
- Death

Patients who discontinue study treatment should NOT be considered withdrawn from the study. They should return for the EoT visit assessments indicated in Table 7-1. If they fail to return for these assessments for unknown reasons, every effort (e.g. telephone, email, letter) should be made to contact them as specified in Section 7.1.8.

At the time patients discontinue study treatment, a visit should be scheduled as soon as possible and within 14 days of the last dose of study treatment or within 14 days of the decision to permanently discontinue study treatment, at which time all of the assessments listed for the EoT visit will be performed. If the decision to discontinue study treatment occurs at a regularly scheduled visit, that visit may become the EoT visit rather than having the patient return for an additional visit.

7.1.6 Withdrawal of Consent

Patients may voluntarily withdraw consent to participate in the study for any reason at any time. Withdrawal of consent occurs only when a patient does not want to participate in the study any longer, and does not want any further visits or assessments, and does not want any further study related contact.

Novartis will continue to retain and use all research results that have already been collected for the study evaluation. All biological samples that have already been collected may be retained and analyzed at a later date (or as required by local regulations).

If a patient withdraws consent, the investigator must make every effort (e.g. telephone, e-mail, letter) to determine the primary reason for this decision and record this information.

Study treatment must be discontinued and no further assessments conducted.

Further attempts to contact the patient are not allowed unless safety findings require communication or follow up.

7.1.7 Follow up for Safety Evaluations

7.1.7.1 30-day safety FU period

All patients must have safety evaluations for 30 days, after the last dose of study treatment.

Information related to AEs (including concomitant medication taken for ongoing AEs) and ongoing anti-neoplastic treatments will be collected. Data collected should be added to the

Adverse Events eCRF, the Prior and Concomitant Medications eCRF, and the Antineoplastic Therapy Since Discontinuation of Study Treatment eCRF.

All AEs suspected to be related to study drug should be followed up weekly, or as clinically indicated, until resolution or stability (see also Section 8.2.2).

7.1.7.2 Disease progression FU

Any patient who discontinues from study treatment for any reason (except for disease progression, death, withdrawal of consent, lost to follow-up, or study termination) will continue to have tumor assessments, performed every 8 weeks, in the follow-up period until disease progression or start of new anticancer therapy.

Antineoplastic therapies since discontinuation of study drug will be collected during this follow-up period.

[redacted]

7.1.8 Lost to follow-up

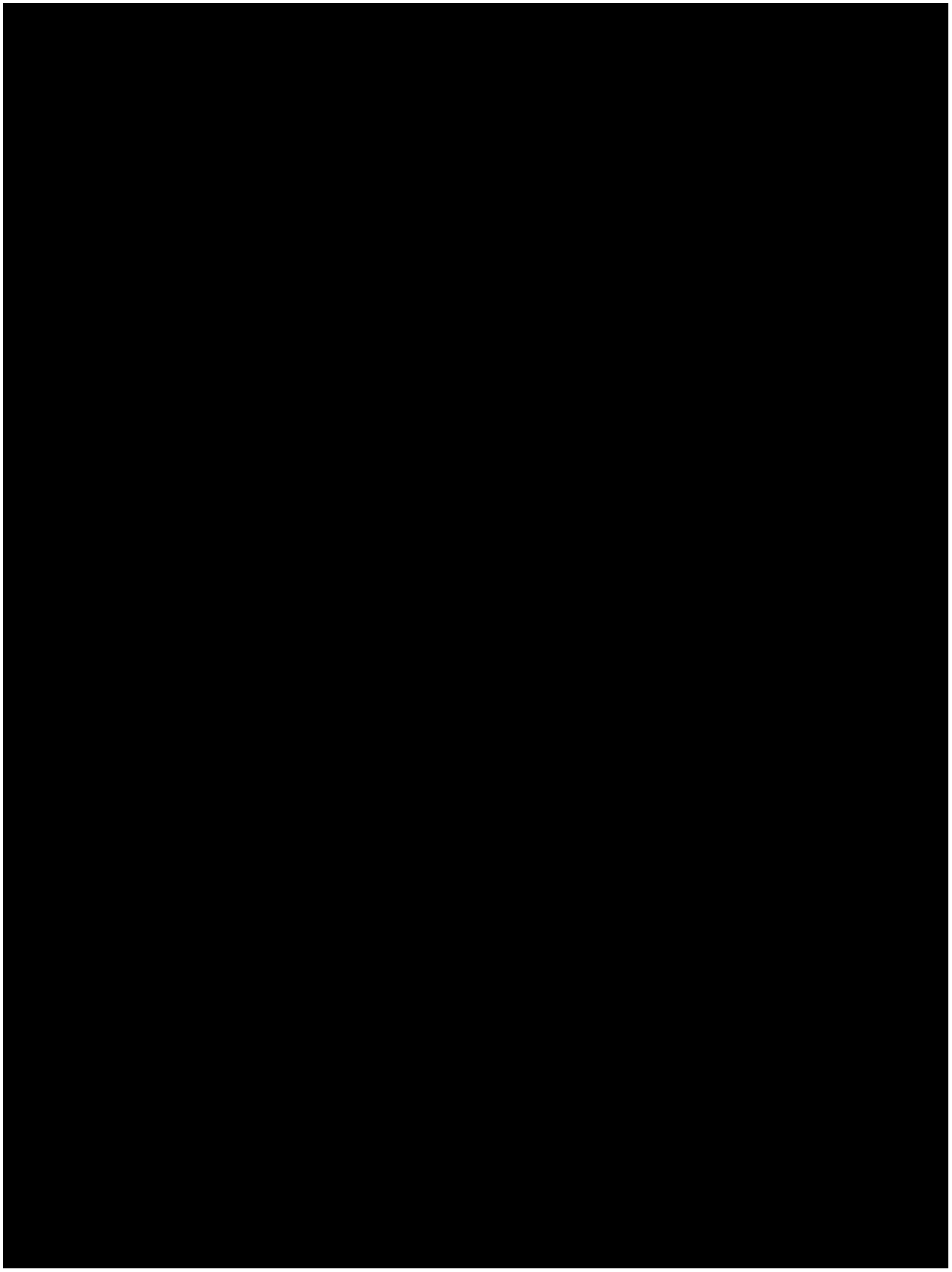
For patients whose status is unclear because they fail to appear for study visits without stating an intention to withdraw consent, the investigator should show "due diligence" by contacting the patient, family or family physician as agreed in the informed consent and by documenting in the source documents steps taken to contact the patient, e.g. dates of telephone calls, registered letters, etc. A patient should not be considered lost to follow-up until due diligence has been completed. Patients lost to follow up should be recorded as such on the appropriate Disposition eCRF.

7.2 Assessment types

7.2.1 Efficacy assessments

Tumor response will be assessed locally according to the Novartis guideline version 3.1 [redacted] based on Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 (Eisenhauer et al 2009). [redacted]

[redacted]



7.2.2 Safety and tolerability assessments

Safety will be monitored by performing physical examinations and assessing vital signs, height and weight, performance status, laboratory evaluations, [redacted] as well as collecting of the adverse events at every visit. For details on AE collection and reporting, refer to Section 8.

7.2.2.1 Physical examination

A complete physical examination will be performed according to the standards at each institution and must be performed as indicated in Table 7-1.

Information about the physical examination must be present in source documentation at the study site. Significant findings that were present prior to the signing of informed consent must be included in the Medical History page on the patient's eCRF. Significant new findings that begin or worsen after informed consent must be recorded on the Adverse Event page of the patient's eCRF.

7.2.2.2 Vital signs

Vital signs (including body temperature, pulse rate and blood pressure) must be performed before and at 1, 3 and 6 hours after dosing, per institutional standards on C1D1, C1D15, [redacted] For all other visits that coincide with PK samples, vital signs should be taken at pre-dose and 1 hour post-dose. For all other visits indicated in Table 7-1, vital signs should be recorded only at pre-dose. Blood pressure and pulse rate measurements should be assessed while the patient is sitting. On the days of blood sampling for PK, the vital signs should be collected prior to the blood collection.

7.2.2.3 Height and weight

Height and body weight (indoor clothing, but without shoes) will be measured. Height will be collected at screening only. Weight will be measured at the visits indicated in Table 7-1. More frequent examinations may be performed at the discretion of the Investigator and if medically indicated.

7.2.2.4 Performance status

ECOG performance status will be assessed as indicated in Table 7-1. The ECOG performance status scale is summarized in Table 7-3.

Table 7-3 ECOG performance status

Grade	ECOG Status
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (e.g., light house work, office work)
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair

7.2.2.5 Laboratory evaluations

All laboratory parameters assessed for safety purposes will be evaluated locally, at the site. Refer to Table 7-4 for a summary of the parameters to be evaluated according to Table 7-1.

At any time during the study, abnormal laboratory parameters which are clinically relevant (e.g., require dose modification and/or interruption of study treatment, lead to clinical symptoms or signs, or require therapeutic intervention), whether specifically requested in the protocol or not, will be recorded on the Adverse Events eCRF page. Laboratory data will be summarized using the CTCAE (version 4.03).

In the case where a laboratory assessment that is listed in the inclusion/exclusion criteria is outside of a protocol-specified range at Screening, the assessment may be repeated prior to first treatment. If the repeat value remains outside of protocol-specified ranges, the patient is excluded from the study.

Novartis must be provided with a copy of the laboratory's certification, and normal ranges for each parameter measured. In addition, if at any time a patient has laboratory parameters obtained from a different outside laboratory, Novartis must be provided with a copy of the certification and normal ranges for that laboratory.

Unscheduled assessment can be performed if clinically indicated.

7.2.2.5.1 Hematology

Hematology panel outlined in Table 7-4 will be performed as per the assessment schedule in Table 7-1.

7.2.2.5.2 Clinical chemistry

Clinical chemistry panel outlined in Table 7-4 will be performed as per the assessment schedule in Table 7-1.

[redacted]

7.2.2.5.3 Coagulation

Coagulation panel outlined in Table 7-4 will be performed as per the assessment schedule in Table 7-1.

An unscheduled coagulation sample may be collected as clinically needed.

7.2.2.5.4 Pregnancy and assessments of fertility

Serum hCG pregnancy tests will be conducted for all female patients of childbearing potential at all visits in the assessment schedule in Table 7-1. The 30 day safety follow up pregnancy test may either be performed by a serum hCG or urine test.

For female adolescent patients of childbearing potential, a urine pregnancy test may be conducted at visits, per the assessment schedule in Table 7-1, when a serum hCG pregnancy test is not permitted due to local regulations.

The pre-dose pregnancy test on C1D1 does not have to be performed if the screening serum pregnancy test was done within 72 hours prior to the first dose and was negative.

[redacted] If a patient becomes pregnant, study treatment must be stopped immediately. If a pregnancy test is positive, but the patient is thought not to be pregnant, study treatment should be stopped until it is determined that the test was falsely positive, and pregnancy is excluded.

7.2.2.6 Cardiac assessments

7.2.2.6.1 Electrocardiogram (ECG)

Standard 12 lead ECG will be performed as per the assessment schedule in Table 7-1 and Table 7-5. For all patients, 3 sequential 12-lead ECGs must be performed during the trial.

[redacted]

Interpretation of the tracing must be made by a qualified physician and documented on the ECG eCRF page. Each ECG tracing should be labeled with the study number, patient initials (where regulations permit), patient number, date, and kept in the source documents at the study site. Clinically significant abnormalities present when the patient signed informed consent should be reported on the Medical History eCRF page. Clinically significant findings must be discussed with Novartis prior to enrolling the patient in the study. New or worsened clinically significant findings occurring after informed consent must be recorded on the Adverse Events eCRF page.

All ECGs will be independently reviewed by a central laboratory. Instructions for the collection and transmission of ECGs to the central ECG laboratory will be provided in the ECG Manual.

[redacted]

Clinically significant abnormalities present at screening should be reported on the Medical History eCRF page. New or worsened clinically significant findings occurring after informed consent must be recorded on the Adverse Events eCRF page. All eligibility and patient management decisions could be made based on the local reading of the ECG exceptionally if the results of the central ECG can't be received in a timely manner (prior to first dose).

[redacted]

7.2.2.6.2 Cardiac imaging - MUGA (multiple gated acquisition) scan or echocardiogram

MUGA scans or ECHO to assess LVEF will be performed as outlined in Table 7-1, within the windows outlined in Section 7.1. Additional assessments may be performed if clinically indicated. A MUGA scan or ECHO will be performed at end of study treatment only if an assessment of LVEF has not been performed ≤ 14 days prior to EoT.

[redacted]

7.2.3 Pharmacokinetics

Serial blood samples should be collected from all patients in dose escalation and dose expansion parts of the study in order to characterize the single dose and steady-state plasma PK of LTT462 after oral administration to patients.

[redacted]

A detailed description of the planned pharmacokinetic analyses is given in Section 10.5.3.

7.2.3.1 Pharmacokinetics and blood collection and handling

PK blood samples will be taken by either direct venipuncture or an indwelling cannula inserted in a forearm vein. At each time point, specified in Table 7-6 and Table 7-7, about 2 mL of blood will be collected into tubes containing K2 EDTA. These tubes should then be gently inverted several times to thoroughly mix the blood with the anticoagulant. Refer to the [CLTT462X2101 Laboratory Manual] for detailed instructions for the collection, handling, and shipment of PK samples.

All sampling time points in Table 7-6 and Table 7-7 are relative to the previous time of LTT462 administration. If the dosing schedule is changed to BID [redacted] (Section 4.1) the time points will follow the same collection plan unless otherwise indicated in the tables.

On the days of PK assessments, the following information should be recorded in the appropriate eCRF and source documents:

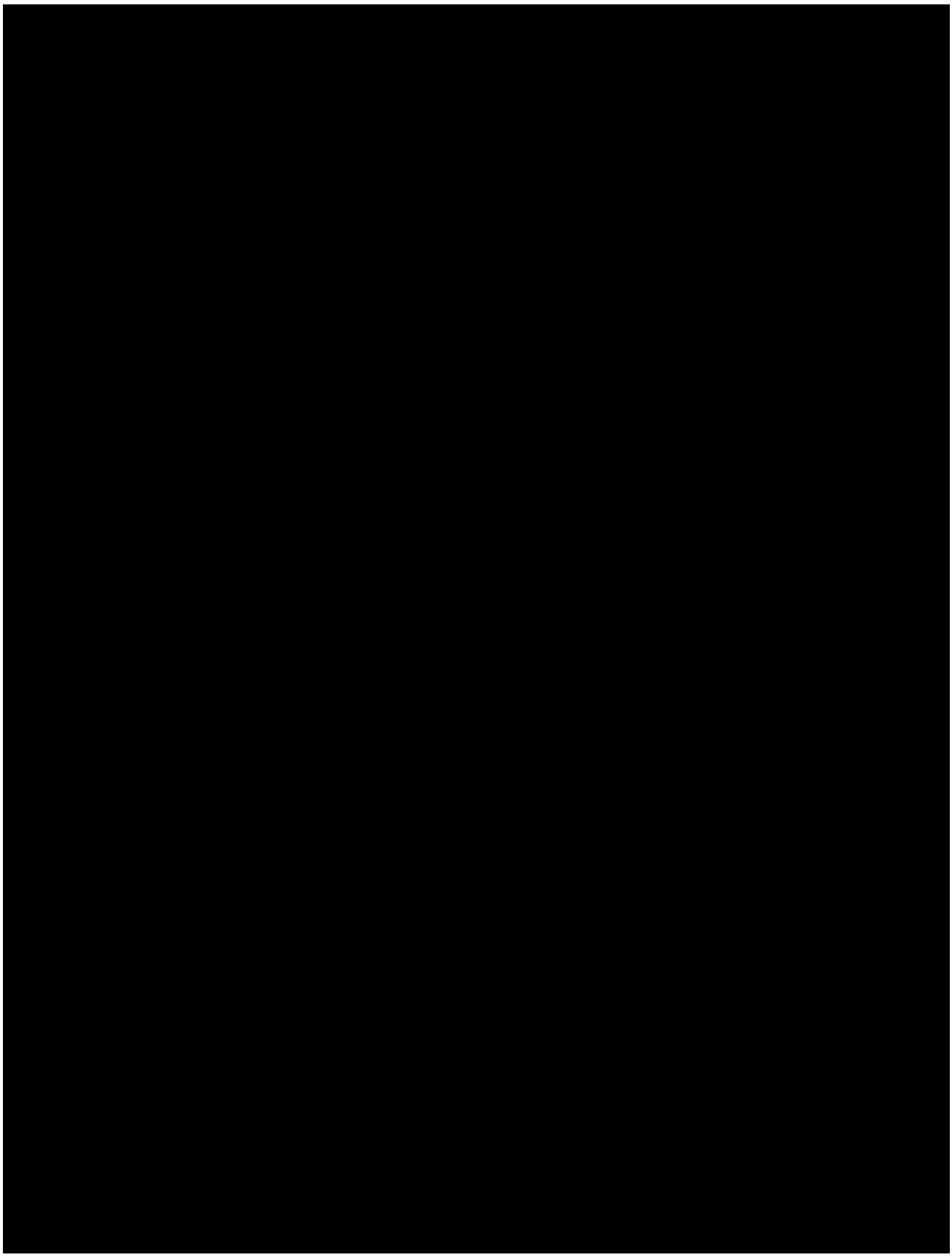
- date and times of drug administration prior to first post-dose blood collection
- date and actual time of PK blood draw
- [redacted]
- time of vomiting, if it occurs within 4 hours following LTT462 administration
- any sampling problems.

On days and time points where blood PD samples are to be drawn, the PK sample should be drawn first.

[redacted]

The date and time of the unscheduled blood sample collection, and the date, time and dose of the LTT462 dose taken prior to the unscheduled blood sample collection should be entered in the appropriate eCRF page.

[redacted]



[redacted]

[redacted]

[redacted]

7.2.4 Biomarkers

In this study biomarker analyses will be used to investigate the effect of LTT462 at the molecular and cellular level as well as to determine how changes in the markers may relate to

exposure and clinical outcomes. [redacted] The sample collection information, as required, should be recorded on the relevant eCRF page(s) and central laboratory requisition form(s).

To the extent possible, actual date of biomarker samples collection should be on the same day as the tumor evaluation when scheduled coincidently. Table 7-8 summarizes the biomarker collections for this study. On days and time points when biomarker and PK blood samples are being collected, the PK sample must be drawn first. If the dosing schedule is changed to BID [redacted] the time points will follow the same collection plan unless otherwise indicated in the table.

Detailed instructions for the collection, handling, and shipping of biomarker samples are outlined in the study [Laboratory Manual].

While the goal of the biomarker assessments is to provide supportive data for the clinical study, there may be circumstances when a decision is made to stop a collection, or not perform or discontinue an analysis due to either practical or strategic reasons (e.g., inadequate sample number, issues related to the quality of the sample or issues related to the assay that preclude analysis, impossibility to perform correlative analyses, etc.). Therefore, depending on the results obtained during the study, sample collection analysis may be omitted at the discretion of Novartis.

Table 7-8 Biomarker sample collection plan

Sample Type	Volume	Visit / Time point	Marker	Purpose
Tumor samples				
Archival Tumor (preferably collected after last antineoplastic treatment)* **or** Newly obtained Tumor biopsy	FFPE block / 11 tissue sections at 4 µm **Or** Newly obtained formalin fixed tumor biopsy in ethanol (3-6 passes)	Molecular pre-screening (Section 7.1.1)	[redacted]	Determine patient eligibility [redacted]
* If existing local data or local testing is used for patient selection, any remaining tumor sample used for patient selection is requested for retrospective analysis if an adequate amount remains. If available, FFPE (formalin fixed paraffin embedded) tissue block (preferred) or 11 unstained slides (4µM) should be submitted at C1D1 after the patient has received their first dose.				
Newly obtained tumor biopsy for biomarker analyses** [redacted]	Newly obtained formalin fixed tumor biopsy in ethanol (3-6 passes/visit)	Screening (newly obtained tumor sample collected at pre-screening may be used if an adequate amount remains) [redacted]	DUSP6 and/or [redacted]	Pharmacodynamic effect in tumor and/or [redacted]

Sample Type	Volume	Visit / Time point	Marker	Purpose
[redacted]		[redacted]	[redacted]	
For adolescent patients only: screening and on treatment biopsies are requested, however exceptions may be granted following documented agreement between Novartis and Investigator.				
[redacted]				
Blood samples				
Whole Blood	[redacted]		DUSP6	Pharmacodynamic effect.

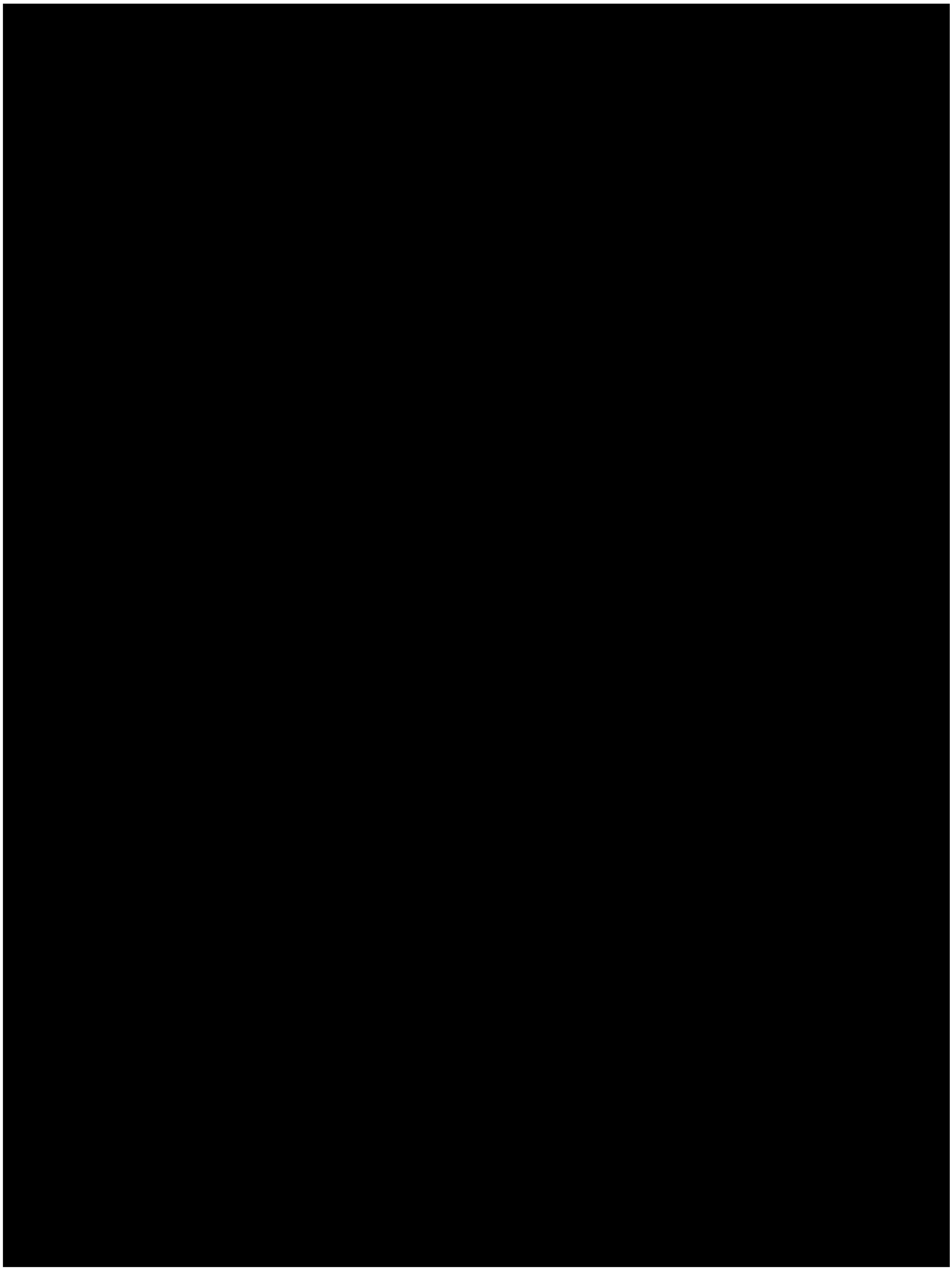
Sample Type	Volume	Visit / Time point	Marker	Purpose
	[redacted]			

[redacted]

7.2.4.1 LTT462 pharmacodynamic assessments

PD effects of LTT462 will be assessed directly in tumor and surrogate tissue.

[redacted]



[redacted]

[redacted]

8 Safety monitoring and reporting

8.1 Adverse events

8.1.1 Definitions and reporting

An adverse event is defined as the appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s), or medical condition(s) that occur after patient's signed informed consent has been obtained.

For patients whose MAPK pathway alteration(s) status is unknown and who sign the molecular pre-screening ICF, AEs which occur after signature of this consent will only be captured if they meet the definition of serious as outlined in Section 8.2 and are reported to be causally related with study procedures (e.g. an invasive procedure such as biopsy). Once the main study ICF is signed, all AEs per the descriptions below will be captured in the Adverse Event eCRF.

Patients for whom the MAPK pathway alteration(s) status is known, and confers eligibility to the study, will sign the main study ICF only. All AEs per the descriptions below will be captured in the Adverse Event eCRF.

Abnormal laboratory values or test results occurring after informed consent constitute adverse events only if they induce clinical signs or symptoms, are considered clinically significant, require therapy (e.g., hematologic abnormality that requires transfusion or hematological stem cell support), or require changes in study medication(s).

Adverse events that begin or worsen after informed consent should be recorded in the Adverse Events eCRF. Conditions that were already present at the time of informed consent should be recorded in the Medical History page of the patient's eCRF. Adverse event monitoring should be continued for at least 30 days following the last dose of study treatment. Adverse events (including lab abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms. When a clear diagnosis cannot be identified, each sign or symptom should be reported as a separate Adverse Event.

Adverse events will be assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03, unless otherwise stated.

If CTCAE grading does not exist for an adverse event, the severity of mild, moderate, severe, and life-threatening, corresponding to Grades 1 - 4, will be used. CTCAE Grade 5 (death) will not be used in this study (but is collected as a seriousness criterion); rather, information about deaths will be collected though a Death form.

The occurrence of adverse events should be sought by non-directive questioning of the patient (subject) during the screening process after signing informed consent and at each visit during the study. Adverse events also may be detected when they are volunteered by the patient (subject) during the screening process or between visits, or through physical examination, laboratory test, or other assessments. As far as possible, each adverse event should be evaluated to determine:

- The severity grade (CTCAE Grade 1-4)
- Its duration (Start and end dates) or Ongoing after the 30 Day safety follow-up
- Its relationship to the study treatment (Reasonable possibility that AE is related: No, Yes)
- Action taken with respect to study or investigational treatment (none, dose adjusted, temporarily interrupted, permanently discontinued, unknown, not applicable)
- Whether medication or therapy was given (no concomitant medication/non-drug therapy, concomitant medication/non-drug therapy)
- Outcome (not recovered/not resolved, recovered/resolved, recovering/resolving, recovered/resolved with sequalae, fatal, unknown)
- Whether it is serious, where a SAE is defined as in Section 8.2.1 and which seriousness criteria have been met.

All adverse events should be treated appropriately. If a concomitant medication or non-drug therapy is given, this action should be recorded on the Adverse Event eCRF.

Once an adverse event is detected, it should be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study treatment, the interventions required to treat it, and the outcome.

Progression of malignancy (including fatal outcomes), if documented by use of appropriate method (for example, as per RECIST criteria for solid tumors), should not be reported as a serious adverse event.

Adverse events separate from the progression of malignancy (example, deep vein thrombosis at the time of progression or hemoptysis concurrent with finding of disease progression) will be reported as per usual guidelines used for such events with proper attribution regarding relatedness to the drug.

8.1.2 Laboratory test abnormalities

8.1.2.1 Definitions and reporting

Laboratory abnormalities that constitute an Adverse event in their own right (are considered clinically significant, induce clinical signs or symptoms, require concomitant therapy or require changes in study treatment), should be recorded on the Adverse Events eCRF. Whenever possible, a diagnosis, rather than a symptom should be provided (e.g. anemia instead of low hemoglobin). Laboratory abnormalities that meet the criteria for Adverse Events should be followed until they have returned to normal or an adequate explanation of the abnormality is found. When an abnormal laboratory or test result corresponds to a sign/symptom of an already reported adverse event, it is not necessary to separately record the lab/test result as an additional event.

Laboratory abnormalities, that do not meet the definition of an adverse event, should not be reported as adverse events. A Grade 3 or 4 event (severe), as per CTCAE, does not automatically indicate a SAE unless it meets the definition of serious, as defined below and/or as per investigator's discretion. A dose hold or medication for the lab abnormality may be required by the protocol in which case the lab abnormality would still, by definition, be an adverse event and must be reported as such.

8.1.3 Adverse events of special interest

These will be determined at a program level on an ongoing basis.

8.2 Serious adverse events

8.2.1 Definitions

Serious adverse event (SAE) is defined as one of the following:

- Is fatal or life-threatening
- Results in persistent or significant disability/incapacity
- Constitutes a congenital anomaly/birth defect
- Is medically significant, i.e., defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above
- Requires inpatient hospitalization or prolongation of existing hospitalization.
  Note that hospitalizations for the following reasons should NOT be reported as serious adverse events:
  - Routine treatment or monitoring of the study indication, not associated with any deterioration in condition.
  - Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent.

  - Social reasons and respite care in the absence of any deterioration in the patient's general condition.
- Note: Treatment on an emergency outpatient basis that does not result in hospital admission and involves an event not fulfilling any of the definitions of a SAE given above is not a serious adverse event.

Progression of underlying malignancy is not reported as an adverse event if it is clearly consistent with the suspected progression of the underlying cancer as defined by RECIST criteria. Hospitalization due solely to the progression of underlying malignancy should NOT be reported as a serious adverse event.

Clinical symptoms of progression may be reported as adverse events if the symptom cannot be determined as exclusively due to the progression of the underlying malignancy, or does not fit the expected pattern of progression for the disease under study.

Symptomatic deterioration may occur in some patients. In this situation, progression is evident in the patient's clinical symptoms, but is not supported by the tumor measurements. Or, the disease progression is so evident that the investigator may elect not to perform further disease assessments. In such cases, the determination of clinical progression is based on symptomatic deterioration. These determinations should be a rare exception as every effort should be made to document the objective progression of underlying malignancy.

If there is any uncertainty about an adverse event being due only to the disease under study, it should be reported as an AE or SAE.

8.2.2 Reporting

For patients with unknown MAPK alteration(s) status and who sign the molecular pre-screening ICF, SAE collection will start upon signing the molecular pre-screening ICF. SAEs will only be reported if the event is suspected to be causally related to a study procedure as assessed by the investigator (e.g. an invasive procedure such as biopsy). SAEs will be followed until resolution or until clinically relevant improvement or stabilization. If the main ICF is not signed (molecular screen failure), SAE collection ends 30 days after the last study related procedure.

For patients with known MAPK alteration(s) status who sign the main study ICF, SAE collection starts at time of main study informed consent whether the patient is a screen failure or not.

To ensure patient safety, every SAE, regardless of suspected causality, occurring after the patient has provided main informed consent and until at least 30 days after the patient has stopped study treatment must be reported to Novartis within 24 hours of learning of its occurrence.

Any additional information for the SAE including complications, progression of the initial SAE, and recurrent episodes must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one should be reported separately as a new event.

Any SAEs experienced after this 30 days period should only be reported to Novartis if the investigator suspects a causal relationship to the study treatment.

Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form; all applicable sections of the form must be completed in order to provide a clinically thorough report. The investigator must assess and record the relationship of each SAE to each specific study treatment (if there is more than one study treatment), complete the SAE Report Form in English, and submit the completed form within 24 hours Novartis. Detailed instructions regarding the submission process and requirements for signatures are to be found in the investigator folder provided to each site.

Follow-up information is submitted in the same way as the original SAE Report. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not, and whether the patient continued or withdrew from study participation.

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the Novartis study treatment, an oncology Novartis Chief Medical Office and Patient Safety (CMO&PS) department associate may urgently require further information from the investigator for Health Authority reporting. Novartis may need to issue an Investigator Notification (IN), to inform all investigators involved in any study with the same drug that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC or as per national regulatory requirements in participating countries.

8.3 Pregnancies

To ensure patient safety, each pregnancy occurring while the patient is on study treatment must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded on a Clinical Trial Pregnancy Form and reported by the investigator to the oncology Novartis CMO&PS. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

Pregnancy outcomes should be collected for the female partners of any males who took study treatment in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

8.4 Warnings and precautions

No evidence available at the time of the approval of this study protocol indicated that special warnings or precautions were appropriate, other than those noted in the provided [LTT462

Investigator Brochure]. Additional safety information collected between Investigator's Brochure updates will be communicated in the form of Investigator Notifications. This information will be included in the patient informed consent and should be discussed with the patient during the study as needed.

8.5 Data Monitoring Committee

A data monitoring board will not be used for this study.

[redacted]

[redacted]

9 Data collection and management

9.1 Data confidentiality

Information about study subjects will be kept confidential and managed under the applicable laws and regulations. Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect follow-up safety information (e.g. has the subject experienced any new or worsened AEs) at the end of their scheduled study period.

The data collection system for this study uses built-in security features to encrypt all data for transmission in both directions, preventing unauthorized access to confidential participant information. Access to the system will be controlled by a sequence of individually assigned user identification codes and passwords, made available only to authorized personnel who have completed prerequisite training.

Prior to entering key sensitive personally identifiable information (Subject Initials and exact Date of Birth), the system will prompt site to verify that this data is allowed to be collected. If the site indicates that country rules or ethics committee standards do not permit collection of these items, the system will not solicit Subject Initials. Year of birth will be solicited (in the place of exact date of birth) to establish that the subject satisfies protocol age requirements and to enable appropriate age-related normal ranges to be used in assessing laboratory test results.

9.2 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, Novartis personnel (or designated Contract Research Organization (CRO)) will review the protocol and CRFs with the investigators and their staff. During the study, the field monitor will visit the site regularly to check the completeness of patient records, the accuracy of entries on the CRFs, the adherence to the protocol to Good Clinical Practice, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits.

The investigator must maintain source documents for each patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or

assessments. All information recorded on CRFs must be traceable to source documents in the patient's file. The investigator must also keep the original signed informed consent form (a signed copy is given to the patient).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the eCRF entries. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria and documentation of SAEs. Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan.

9.3 Data collection

For studies using Electronic Data Capture (EDC), the designated investigator staff will enter the data required by the protocol into the eCRF. The eCRFs have been built using fully validated secure web-enabled software that conforms to 21 CFR Part 11 requirements, Investigator site staff will not be given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies in the eCRFs and, allow modification or verification of the entered data by the investigator staff.

The Principal Investigator is responsible for assuring that the data entered into eCRF is complete, accurate, and that entry and updates are performed in a timely manner.

PK and biomarker (blood, serum, plasma and/or tissue) samples obtained during the course of the study will be collected from the Investigator sites and analyzed by Novartis designated laboratories. ECG data collected during the study will be reviewed and processed centrally by a specialist CRO. Radiological and photography data will be acquired by the sites and interpreted locally, however, during the course of the study, Novartis may decide to have a central review of the radiological assessments performed. In such case, the investigator's staff will be instructed on how to send data from these radiological assessments to a CRO for central review when needed. Details regarding all CRO procedures including collection and shipment of data will be described in the manual provided by the respective CRO. Designated investigational site staff will enter the information required by the protocol into the appropriate eCRF and/or designated laboratory requisition forms. Field monitors will review the eCRFs and laboratory paper requisition forms for accuracy and completeness and instruct site personnel to make any required corrections or additions. One copy of the requisition form will be forwarded to each analytical laboratory with the respective sample(s) by the field monitor or by the designated investigational site staff; and one copy will be retained at the investigational site.

9.4 Database management and quality control

For studies using eCRFs, Novartis personnel (or designated CRO) will review the data entered by investigational staff for completeness and accuracy. Electronic data queries stating the nature of the problem and requesting clarification will be created for discrepancies and missing values and sent to the investigational site via the EDC system. Designated investigator site staff are required to respond promptly to queries and to make any necessary changes to the data.

Concomitant treatments and prior medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification

system. Medical history/current medical conditions and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

ECG, PK, and biomarker samples and/or data will be processed centrally and the results will be sent electronically to Novartis (or a designated CRO).

At the conclusion of the study, the occurrence of any protocol violations will be determined. After these actions have been completed and the data has been verified to be complete and accurate, the database will be declared locked. Authorization is required prior to making any database changes to locked data, by joint written agreement between the Global Head of Biostatistics and Data Management and the Global Head of Clinical Development.

For EDC studies, after database lock, the investigator will receive a CD-ROM or paper copies of the patient data for archiving at the investigational site.

10 Statistical methods and data analysis

Study data will be analyzed by Novartis and/or designated CRO. Any data analysis carried out independently by the investigator must be submitted to Novartis before publication or presentation.

Study data will be summarized with respect to demographic and baseline characteristics, efficacy observations and measurements, safety observations and measurements, pharmacokinetics and PD measurements, using descriptive statistics (quantitative data) and contingency tables (qualitative data). All data from participating centers in this protocol will be combined, so that an adequate number of patients will be available for analysis.

Summaries will be produced by treatment group for the dose escalation part, by study arm for the expansion part, and overall. Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, minimum, and maximum will be presented.

The primary CSR will include all patients' data reported in the study up to the time when all patients have had the opportunity to complete at least 6 cycles of treatment or discontinued the study. Any additional data reported past this data cutoff date for the primary CSR will be reported in a closeout CSR once all study patients have discontinued the study (refer to Section 4.3).

The following rules will be followed for reporting results unless stated otherwise:

a. Dose escalation: cohorts with the same dose level , regimen, [redacted] will be pooled into a single treatment group. All tables, figures and analyses will be produced by treatment group.

[redacted]

10.1 Analysis sets

10.1.1 Full Analysis Set

The Full Analysis Set (FAS) includes all patients who received at least one dose (full or partial) of LTT462. Patients will be analyzed according to the treatment assigned.

10.1.2 Safety Set

The Safety Set includes all patients who received at least one dose (full or partial) of LTT462. Patients will be analyzed according to the treatment received, where treatment received is defined as:

- The treatment assigned, if it was received at least once or
- The first study treatment received, if the treatment assigned was never received.

[redacted]

10.1.4 Dose-determining analysis set

The DDS includes all patients from the Safety Set (escalation part) who met the minimum exposure criterion and had sufficient safety evaluations, or experienced a DLT during the first 28 days of dosing.

A patient has met the minimum exposure criterion when exposed to the received study treatment (as defined in the Safety Set definition above) for at least 75% of the planned LTT462 total daily doses in the first cycle of treatment.

- For QD: at least 75% percent of the planned daily doses means at least 21/27, given that the C1D2 dose will be omitted.

[redacted]

- For BID: at least 75% of planned BID daily doses means at least 20/26 full days of dosing of the planned doses, given the C1D2 dose will be omitted and a single dose will be administered on the first day of treatment.

Patients who do not experience a DLT during the first cycle of dosing are considered to have sufficient safety evaluations if they have been observed for ≥ 28 days following the first dose, and are considered by both the Sponsor and Investigators to have enough safety data to conclude that a DLT did not occur.

10.1.5 Pharmacokinetic analysis set

- The Pharmacokinetic Analysis Set (PAS) consists of all patients who have at least one PK blood sample providing measurable LTT462 and who satisfy the bullets below: Patient received at least one dose of study treatment
- Patient followed the dosing recommendation (Section 6.1.1) and took the drug 1 hour before or 2 hours after the meal

- Patient did not vomit within 4 hours of dose administration
- Patient provided at least one primary PK parameter

[redacted]

10.2 Patient demographics/other baseline characteristics

Demographic and other baseline data will be presented descriptively. Demographic data includes age, gender, race, height, weight, ECOG performance status. Baseline data includes diagnosis and extend of cancer, smoking and medical history, and current (ongoing) medical conditions, including cancer-related conditions and symptoms, and prior anti-neoplastic therapy (medication, radiotherapy, or surgery summarized separately).

Medical history and current medical conditions are coded using the latest MedDRA terminology.

Summary tables and listings will be based on the FAS.

[redacted]

10.4 Primary objective

The primary objective of this study is to characterize the safety and tolerability of LTT462 and identify a recommended dose and regimen for future studies.

10.4.1 Variable

The primary endpoints defined to evaluate the safety of LTT462 are incidence and severity of AEs, changes in hematology and chemistry laboratory values, changes vital signs, changes in ECG and incidence and nature of DLTs (dose escalation only). Tolerability will be evaluated in terms of dose interruptions, dose reductions, and dose intensity.

10.4.2 Statistical hypothesis, model, and method of analysis

DLTs will be analyzed using a Bayesian model. The incidence of DLTs will be summarized by system organ class and preferred term. The DDS will be used to analyze DLTs. Statistical analysis of endpoints other than DLTs will be descriptive, based on the safety analysis set, no hypotheses or models will be considered. Descriptive statistics will be provided on:

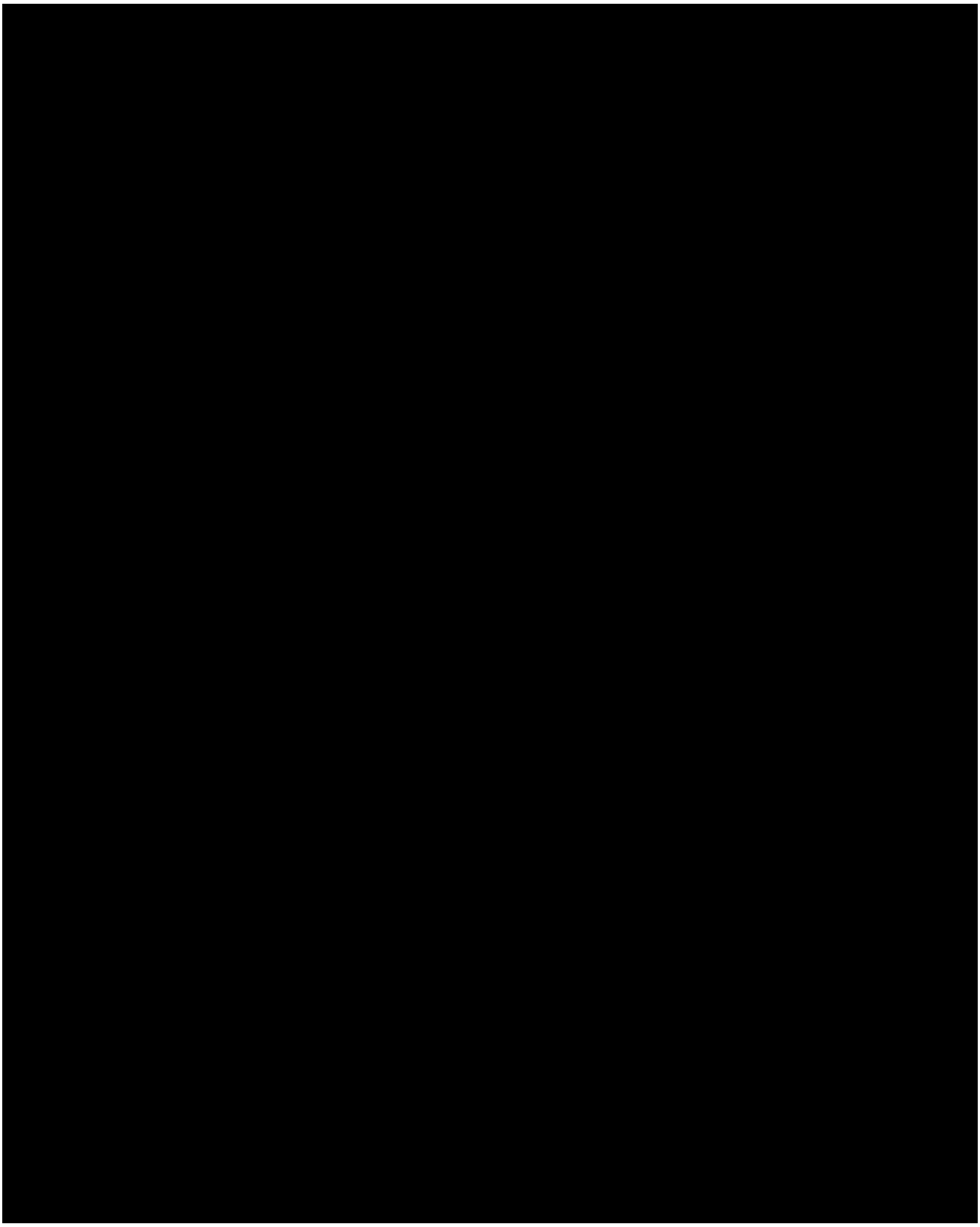
- The incidence by patients of AEs**,** independent of relationship to study drug, and also considering severity
- The incidence by patient of serious AE, independent of relationship to study drug
- Changes from baseline to worst post-baseline hematology and chemistry laboratory values
- Changes from baseline to worst post-baseline values of ECG parameters
- Changes in vital signs from baseline to worst post-baseline values
- Summary of dose intensity, and number and percentage of dose interruptions and reductions.

10.4.2.1 Dose limiting toxicities (dose escalation)

Dosing regimens QD [redacted]

The dose escalation will be guided by a BHLRM based on the first Cycle DLT data of the study treatment. This model estimates the relationship between dose and the probability of a patient experiencing a DLT following a QD regimen [redacted]

[redacted]



Additional dosing regimen

Should emergent data support the investigation of [redacted] a separate BLRM, guided by the EWOC principle, will be used to make dose recommendations.

[redacted]

Dose recommendation

After each cohort of patients, the posterior distributions for the probabilities of DLT rates at different dose levels will be obtained. Dose recommendation will be based on posterior summaries including the mean, median, standard deviation, 95%-credible interval, and the probability that the true DLT rate for each dose lies in one of the following categories:

- [0,16%) under-dosing
- [16%,33%) targeted toxicity
- [33%,100%] excessive toxicity

Dose recommendation will also be guided by the EWOC principle, which mandates the dose for the next cohort to have less than 25% chance of excessive toxicity. The final estimate of the MTD/RDE will also satisfy this condition.

Summary of DLTs

A summary of the posterior probabilities of DLT rates in the different toxicity categories and the corresponding illustration will be presented at each dose escalation meeting. For the CSR, DLTs will be listed and the incidence summarized by primary system organ class and preferred term. The dose-determining analysis set will be used.

10.4.2.2 Adverse events

Data handling

AEs will be coded using the latest version of the MedDRA and graded using the CTCAE version 4.03. The CTCAE grade 5 (death) will not be used in this study.

A patient with multiple CTCAE grades for an AE will be summarized under the maximum grade recorded for the event. A subject with multiple occurrences of an AE is counted only once in the AE category (e.g. system organ class, preferred term).

[redacted]

10.4.2.3 Laboratory parameters

Data handling

All laboratory values will be converted into SI units, as appropriate, and the severity grade calculated using CTCAE, version 4.03. For laboratory tests covered by CTCAE, a Grade 0 will be assigned for all non-missing values not graded as 1 or higher. Grade 5 will not be used. For laboratory tests where grades are not defined by CTCAE, results will be graded by the low/normal/high classifications based on local laboratory normal ranges. The list of parameters with CTCAE grading and LNR is presented in Section 10.5.3. [redacted]

[redacted]

10.4.2.4 Electrocardiograms

Data handling

- Unscheduled ECGs are included in the analysis of notable value.
- Triplicate 12 lead sequential readings will be performed at baseline and post-baseline for a patient at the given time points (Section 7.2.2.6), all individual values are transferred, in which case, ECGs are averaged over the patient and then across patients for change from baseline analysis.
- No adjustment (in the variance) is made to account for different patients having differing number of ECGs being averaged at a given time point. (It is assumed that the scheduled assessments for each patient are the same and any deviations are sporadic and minor).

10.4.2.5 Vital signs

Data handling

Change from baseline will only be summarized for patients with both baseline and post-baseline values.

10.4.2.6 Tolerability

Tolerability of study drug treatment will be assessed by summarizing the number and percentage of dose interruptions and dose reductions per patient, together with reasons for dose interruption and dose reductions. Dose intensity and relative dose intensity of LTT462 per patient will be summarized. For relative dose intensity, the number and proportion of patients within the following categories will be presented: < 0.5, ≥ 0.5 - < 0.75, ≥ 0.75 - < 0.9, ≥ 0.9 - < 1.1 and ≥ 1.1.

10.4.3 Handling of missing values/censoring/discontinuations

No imputation for missing data will be performed. Patients with missing baseline assessments will be excluded from analyses where a baseline value is required to compute the corresponding endpoint.

10.4.4 Supportive analyses

During the course of the study, additional analyses may be identified based on emerging safety data, to support the primary analyses. These analyses will be defined in the statistical analysis plan prior to clinical database lock.

10.5 Secondary objectives

10.5.1 Secondary efficacy objectives

Tumor response will be determined locally according to RECIST v1.1 (refer to Appendix 1) per local investigators' assessment. The FAS will be used for all efficacy analyses.

Efficacy endpoints are progression free survival (PFS), ORR, duration of response (DOR), and DCR. [redacted]

Dose escalation part

For the dose escalation part, the best overall response (BOR) and individual lesions, and the PFS time will be presented for each patient in a listing.

[redacted]

[redacted]

10.5.2 Secondary Safety objectives

10.5.2.1 Analysis set and grouping for the analyses

For all safety analyses, the safety set will be used. All tables will be presented by treatment group for the dose escalation part and by study group for the dose expansion part.

The overall observation period will be divided into three mutually exclusive segments:

- pre-treatment period: from day of patient's informed consent to the day before first dose of study medication
- on-treatment period: from day of first dose of study medication to 30 days after last dose of study medication
- post-treatment period: starting at day 30+1 after last dose of study medication.

10.5.2.2 Adverse events (AEs)

Analysis of adverse events will be described similar to the primary endpoint. Summary tables for adverse events (AEs) will include only on-treatment events. The listing of all AE will include all AE reported in the study, without date restrictions.

The incidence of the following treatment-emergent adverse events will be summarized by maximum severity (based on CTCAE grades), system organ class and/or preferred term: AE suspected to be study drug related, AE leading to study drug discontinuation, AE requiring drug dosage adjustments/temporarily interrupted, SAE suspected to be study drug related.

Deaths with onset on-treatment and also all deaths occurring during the study will be summarized by system organ class and/or preferred term. AE which are not SAE will be summarized by primary system organ class and preferred term.

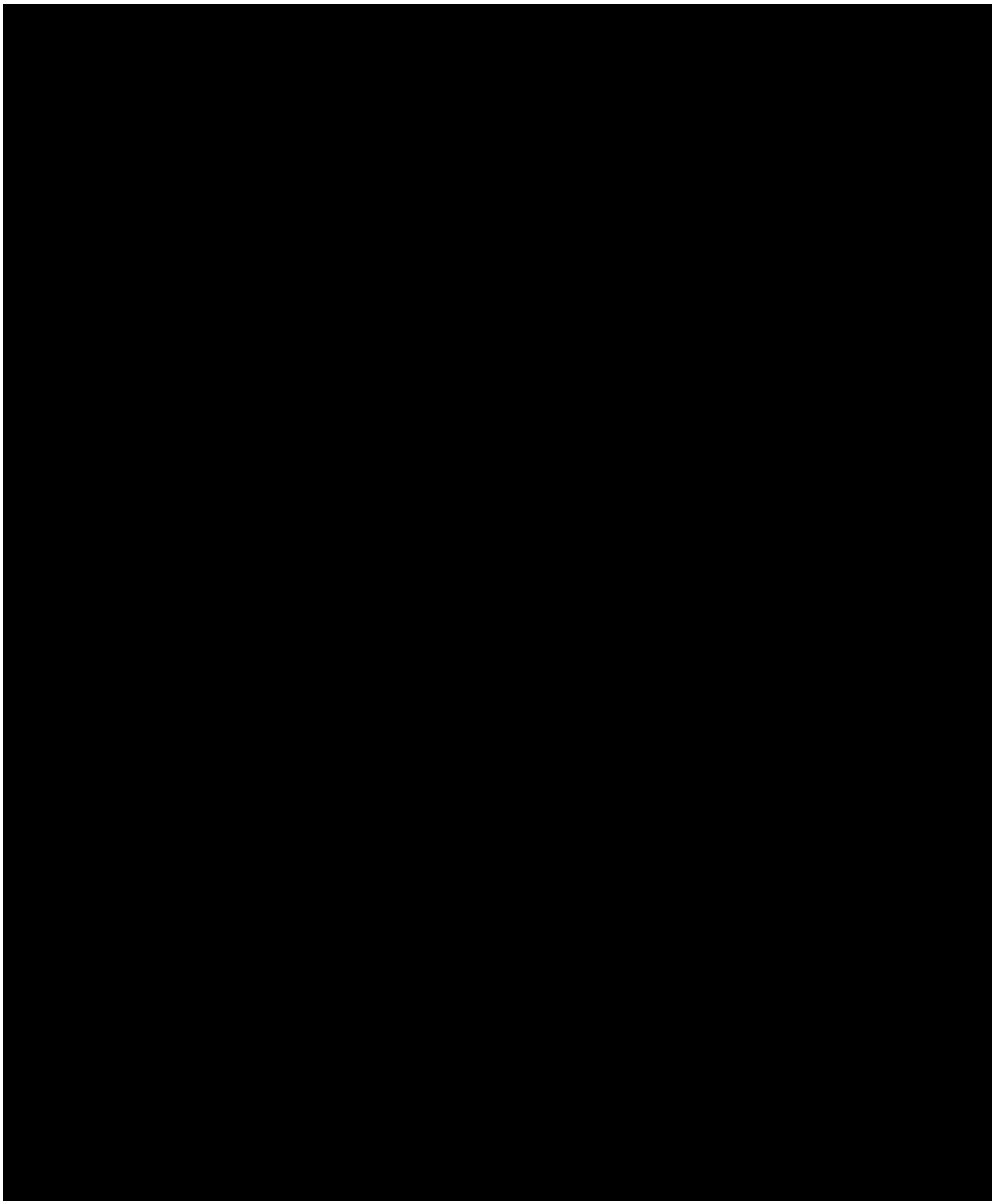
LTT462 specific safety event categories (SEC) may be considered. Such categories consist of one or more well-defined safety events which are similar in nature and for which there is a specific clinical interest in connection with the study treatment.

For each specified SEC, number and percentage of patients with at least one event part of the SEC will be reported.

10.5.2.3 Laboratory abnormalities

All laboratory values will be converted into SI units, as appropriate, and the severity grade calculated using CTCAE, version 4.03. Data handling will be as described in Section 10.4.2. Analysis of chemistry and hematology tests results are described in Section 10.4.2. A listing of patients with abnormal values of CTCAE grade 3 or 4 will be presented (for all laboratory parameters measured). For parameters (independent of the test category) with no CTCAE grade, a listing of patients with abnormal values will be provided, with low/high values flagged. [redacted]

[redacted]



10.5.2.4 Hepatic abnormalities

Hepatic abnormalities will be assessed based on the following liver function tests: ALT, AST, ALP, and total bilirubin (TBL). The number and percentage of patients with newly occurring

notable hepatic laboratory values within the categories presented below will be provided. For the combined criteria, shift tables to compare baseline to the worst post-baseline will be presented. A listing of patients with at least one newly occurring notable event will be provided.

[redacted]

10.5.2.5 Other safety data

Other safety assessments include ECOG performance status, physical examinations, height, pregnancy test, MUGA scan or ECHO, [redacted]

[redacted]

[redacted]

10.5.2.6 Supportive analyses for secondary objectives

Refer to Section 10.4.4.

10.5.3 Pharmacokinetics

Pharmacokinetic parameters will be determined by non-compartmental method(s) using the pharmacokinetic profile of LTT462. PK parameters listed in Table 10-7 will be derived and reported, when feasible.

Further analyses may be conducted using population PK approaches. In addition, a model based approach may be used to explore the potential relationship between efficacy, safety, and/or biomarker endpoints and LTT462 concentration and/or exposure metrics. Any analyses performed will be specified either in the study analysis plan or in a stand-alone analysis plan document. All analyses will be reported either in the CSR or a stand-alone report.

Table 10-7 Noncompartmental pharmacokinetic parameters

AUC_{last}	The AUC from time zero to the last measurable concentration sampling time (T_{last}) (mass x time x volume^{-1})
AUC_{tau}	The AUC calculated to the end of a dosing interval (tau) at steady-state (amount x time x volume^{-1})
AUC_{inf}	The AUC from time zero to infinity (mass x time x volume^{-1})
C_{max}	The maximum (peak) observed plasma, blood, serum, or other body fluid drug concentration after single dose administration (mass x volume^{-1})
T_{max}	The time to reach maximum (peak) plasma, blood, serum, or other body fluid drug concentration after single dose administration (time)
C_{min}	Observed concentration at the end of a dosing interval (taken directly before next administration)
CL/F	The total body clearance of drug from the plasma (volume x time^{-1})
Racc	Accumulation ratio calculated using AUC_{tau} at steady state divided by AUC_{tau} at Day 1
T½	Effective elimination half-life

10.5.3.1 Data handling principles

All concentrations below the lower limit of quantitation (LLOQ) or missing data will be labeled as such in the concentration data listings. Concentrations below the LLOQ will be treated as zero in summary statistics and for the calculation of pharmacokinetic parameters, unless otherwise stated under the Pharmacokinetic Analysis Set.

At the time of analysis, concentration data from patients may be removed from the estimation of certain PK parameters depending on the number of available blood samples, concomitant medications, vomiting, etc. Specific time points might be removed from the analysis set if

technical issues with the sample are reported (e.g. sampling issues, missing information). These patients and concentration data points will be identified at the time of analysis

10.5.3.1.1 Data analysis set

All pharmacokinetic data analyses and PK summary statistics will be based on PAS. Only PK blood samples with date and time and for which the last prior dose dates and times are adequately recorded will be included in the PK analyses.

10.5.3.1.2 Basic tables, figures, and listing

Descriptive statistics such as arithmetic and/or geometric mean and CV%, median and range, will be presented for all pharmacokinetic parameters, as applicable. Zero concentrations will not be included in the geometric mean calculations. T_{max} will be summarized in terms of median values and ranges. Missing concentrations or PK parameter values will not be imputed. A listing of derived PK parameters per patient will be produced by treatment group.

Mean plasma concentration versus time profile plots will be generated for LTT462. Further graphical exploratory analyses (such as individual plasma concentration versus time) will be carried out if deemed appropriate.

10.5.3.2 Dose proportionality

The analysis of dose proportionality will be conducted for AUC and C_{max} of LTT462 using a power model on log-transformed scale. The log-transformed PK parameters will each be regressed onto a fixed factor for log (dose). The 90% confidence interval (CI) of the slope for each PK parameter will be computed from the model and presented in a summary table. Dose-proportionality will only be investigated if at least three doses of LTT462 are investigated.

Exploratory analysis will be carried out if deemed necessary.

[redacted]

10.5.3.4 Time-dependency

If AUC_{inf} can be reliably estimated on Day 1, the time dependence of the PK (comparison within subject of Day 1 AUC_{inf} with Day 15 AUC_{tau} with point estimates and CI) will be analyzed. Details will be included in the study analysis plan.

[redacted]

[redacted]

10.5.4 Biomarkers

Since this clinical trial was not designed to address specific biomarkers-related hypotheses, the analysis of this data should be viewed as [redacted] hypotheses generating.

Secondary objectives include the assessment of the PD effect of LTT462 in both tumor and blood of LTT462. For assessment of PD effects of LTT462 in tumor, pre- and post- treatment tumor biopsies will be examined for expression of DUSP6. For assessment of PD effects in blood, levels of DUSP6 will be measured in samples isolated concomitantly with those collected for PK measurements.

10.5.4.1 Outline of the data analysis

Changes in biomarkers in blood and tumor samples may be summarized by means of descriptive analysis and correlation with clinical response and exposure where feasible. If the number of samples is inadequate to perform a rigorous data analysis, then the available data will only be listed.

Additional analyses will be specified in a separate analysis plan and may be reported in the CSR. These analyses may include but are not limited to the meta-analysis of data from this study combined with data from other studies or the analysis of biomarkers generated from samples collected during the study but analyzed after the database lock and completion of the CSR.

10.5.4.2 Data handling principles

For change from baseline analyses, calculations will only be performed on patients with measurable samples and pre- and post- treatment time points. If both the baseline and post baseline values are below the LLOQ, percent change, absolute change, or fold-change from baseline will not be imputed.

10.5.4.3 Data analysis principles

10.5.4.3.1 Analysis sets

The FAS will be used for all biomarker related analyses. The number of patients with measureable samples will be identified in the summaries and relevant proportions will be calculated against this number.

10.5.4.3.2 Basic tables, figures and listings

Baseline and percentage change from baseline in delta Ct (ΔCT) values of DUSP6 expression will be summarized by treatment.

A waterfall plot will be used to depict the change from baseline in ΔCT values of DUSP6 expression (both tumor and blood samples) and annotated with the best overall response.

The best percentage change in tumor size and best overall response will also be displayed as a waterfall plot, annotated with MAPK pathway gene alterations at baseline.

Change from baseline in Dual Specificity Phosphatase 6 (DUSP6) expression

To assess the drug effect on MAPK signaling and correlation to preliminary anti-tumor response, changes of molecular status of DUSP6 in pre- and post-treatment tumor biopsies and blood samples will be analyzed. Percentage and fold changes will be listed.

[redacted]

10.5.4.3.3 Advanced analysis methods

Additional analyses that may be performed after the completion of the final CSR will be documented in separate analysis reports. These analyses may include but are not limited to the meta-analysis of data from this study combined with data from other studies or the analysis of biomarkers generated from samples collected during the study but analyzed after the database lock and completion of the CSR. The data analysis will be described in a separate analysis plan document and may be included in the CSR.

[redacted]

10.7 Interim analysis

No formal interim analyses are planned. However, the dose escalation design foresees that decisions based on the current data are taken before the end of the study. More precisely, after

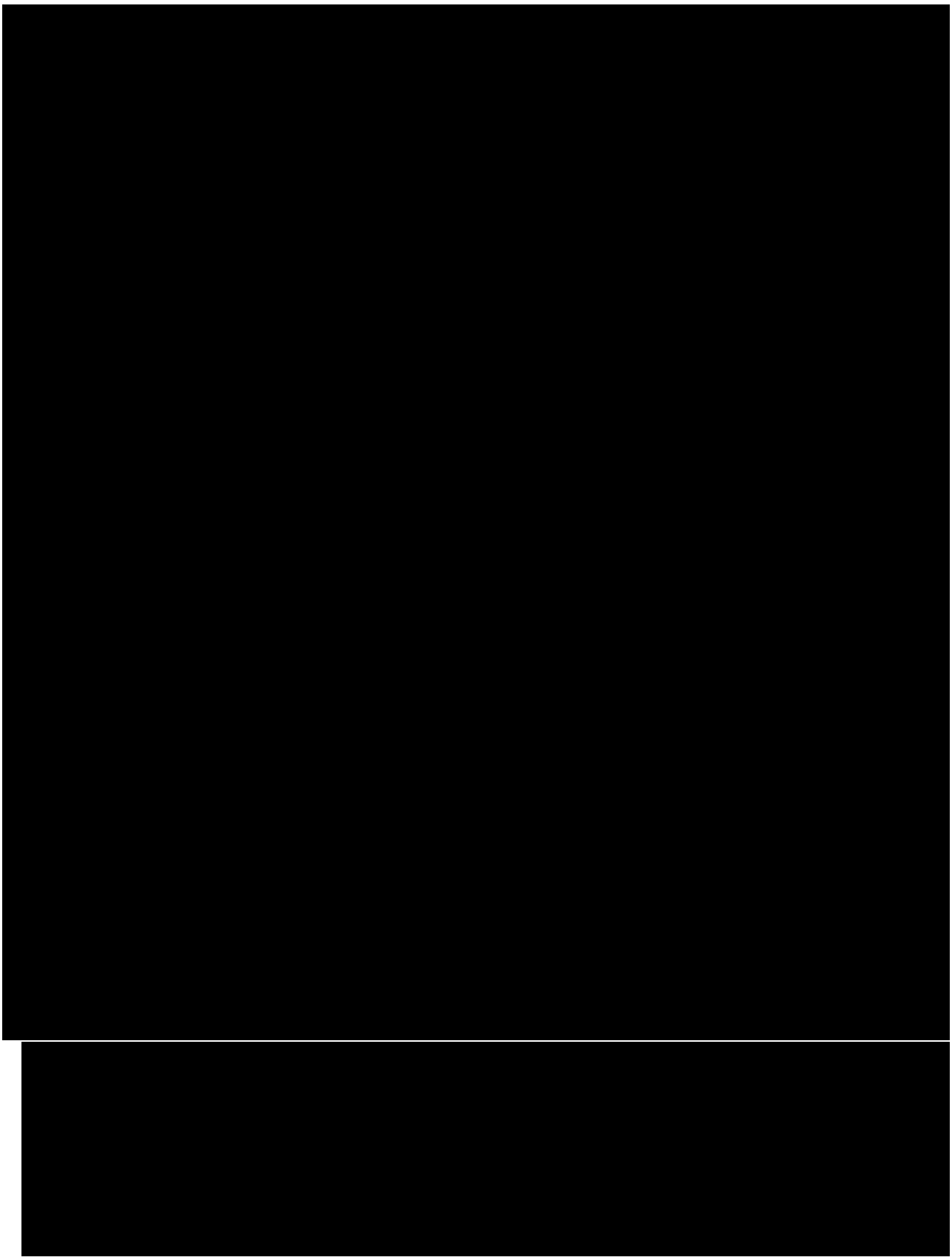
each cohort in the dose escalation part, the next dose of LTT462 has to be chosen depending on the observed data. Details of this procedure and the process for communication with Investigators are provided in Section 6.2.3.

[redacted] Cumulative study data (including safety, tolerability, preliminary anti-tumor activity, PK, and PD) will be reviewed on an ongoing basis by Novartis and study investigators.

10.8 Sample size calculation

10.8.1 Dose-escalation part

Initially, cohorts of 1 to 3 evaluable patients will be enrolled in the dose-escalation part. Upon observation of specific toxicities (see Section 6.2.3 for details), cohorts of 3 to 6 evaluable patients will be enrolled including at least six patients at the MTD/RDE level, as described in Section 6.2.3. Multiple cohorts may be sequentially enrolled to the same dose level. Additional cohorts of 1 to 6 patients may be enrolled at any dose level below the estimated MTD/RDE for further elaboration of safety and pharmacokinetic parameters as required. At least 21 patients are expected to be treated in the dose escalation part, for the model to have reasonable operating characteristics relating to its MTD recommendation. In the event that a lower dose is recommended for the use in the dose expansion without identification of the MTD, then the sample size may be smaller than 21.



11 Ethical considerations and administrative procedures

11.1 Regulatory and ethical compliance

This clinical study was designed, shall be implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC and US Code of Federal Regulations Title 21), and with the ethical principles laid down in the Declaration of Helsinki.

11.2 Responsibilities of the investigator and IRB/IEC/REB

The protocol and the proposed informed consent form must be reviewed and approved by a properly constituted Institutional Review Board/Independent Ethics Committee/Research Ethics Board (IRB/IEC/REB) before study start. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Clinical Quality Assurance representatives, designated agents of Novartis, IRBs/IECs/REBs and regulatory authorities as required.

11.3 Informed consent procedures

Eligible patients may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/IEC/REB-approved informed consent, or, if incapable of doing so, after such consent has been provided by a legally acceptable representative of the patient. In cases where the patient's representative gives consent, the patient should be informed about the study to the extent possible given his/her understanding. If the patient is capable of doing so, he/she should indicate assent by personally signing and dating the written informed consent document or a separate assent form.

For Japan only, written consent is necessary both from the patient and his/her legal representative if he/she is under the age of 20 years.

Informed consent must be obtained before conducting any study-specific procedures (i.e. all of the procedures described in the protocol). The process of obtaining informed consent should be

documented in the patient source documents. The date when a subject's Informed Consent was actually obtained will be captured in their CRFs.

Novartis will provide to investigators, in a separate document, a proposed informed consent form (ICF) that is considered appropriate for this study and complies with the ICH GCP guideline and regulatory requirements. Any changes to this ICF suggested by the investigator must be agreed to by Novartis before submission to the IRB/IEC/REB, and a copy of the approved version must be provided to the Novartis monitor after IRB/IEC/REB approval.

Women of child bearing potential should be informed that taking the study medication may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirement for the duration of the study. If there is any question that the patient will not reliably comply, they should not be entered in the study.

11.4 Discontinuation of the study

Novartis reserves the right to discontinue this study under the conditions specified in the clinical study agreement. Specific conditions for terminating the study are outlined in Section 4.4.

11.5 Publication of study protocol and results

Novartis is committed to following high ethical standards for reporting study results for its innovative medicine, including the timely communication and publication of clinical trial results, whatever their outcome. Novartis assures that the key design elements of this protocol will be posted in a publicly accessible database such as www.clinicaltrials.gov before study start. In addition, results of interventional clinical trials in adult patients are posted on www.novartisclinicaltrials.com, a publicly accessible database of clinical study results within 1 year of study completion (i.e., LPLV), those for interventional clinical trials involving pediatric patients within 6 months of study completion.

Novartis follows the ICMJE authorship guidelines (www.icmje.org) and other specific guidelines of the journal or congress to which the publication will be submitted

Authors will not receive remuneration for their writing of a publication, either directly from Novartis or through the professional medical writing agency. Author(s) may be requested to present poster or oral presentation at scientific congress; however, there will be no honorarium provided for such presentations.

As part of its commitment to full transparency in publications, Novartis supports the full disclosure of all funding sources for the study and publications, as well as any actual and potential conflicts of interest of financial and non-financial nature by all authors, including medical writing/editorial support, if applicable.

For the Novartis Guidelines for the Publication of Results from Novartis-sponsored Research, please refer to www.novartis.com.

11.6 Study documentation, record keeping and retention of documents

Each participating site will maintain appropriate medical and research records for this trial, in compliance with Section 4.9 of the ICH E6 GCP, and regulatory and institutional requirements for the protection of confidentiality of subjects. As part of participating in a Novartis-sponsored study, each site will permit authorized representatives of the sponsor(s) and regulatory agencies to examine (and when required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits and evaluation of the study safety and progress.

Source data are all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Examples of these original documents and data records include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, and subject files and records kept at the pharmacy, at the laboratories, and medico-technical departments involved in the clinical trial.

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site Principal Investigator. The study case report form (CRF) is the primary data collection instrument for the study. The investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported in the CRFs and all other required reports. Data reported on the CRF, that are derived from source documents, should be consistent with the source documents or the discrepancies should be explained. All data requested on the CRF must be recorded. Any missing data must be explained. Any change or correction to a paper CRF should be dated, initialed, and explained (if necessary) and should not obscure the original entry. For eCRFs an audit trail will be maintained by the system. The investigator should retain records of the changes and corrections to paper CRFs.

The investigator/institution should maintain the trial documents as specified in Essential Documents for the Conduct of a Clinical Trial (ICH E6 Section 8) and as required by applicable regulations and/or guidelines. The investigator/institution should take measures to prevent accidental or premature destruction of these documents.

Essential documents (written and electronic) should be retained for a period of not less than fifteen (15) years from the completion of the Clinical Trial unless Sponsor provides written permission to dispose of them or, requires their retention for an additional period of time because of applicable laws, regulations and/or guidelines.

11.7 Confidentiality of study documents and patient records

The investigator must ensure anonymity of the patients; patients must not be identified by names in any documents submitted to Novartis. Signed informed consent forms and patient enrollment log must be kept strictly confidential to enable patient identification at the site.

11.8 Audits and inspections

Source data/documents must be available to inspections by Novartis or designee or Health Authorities.

11.9 Financial disclosures

Financial disclosures should be provided by study personnel who are directly involved in the treatment or evaluation of patients at the site - prior to study start.

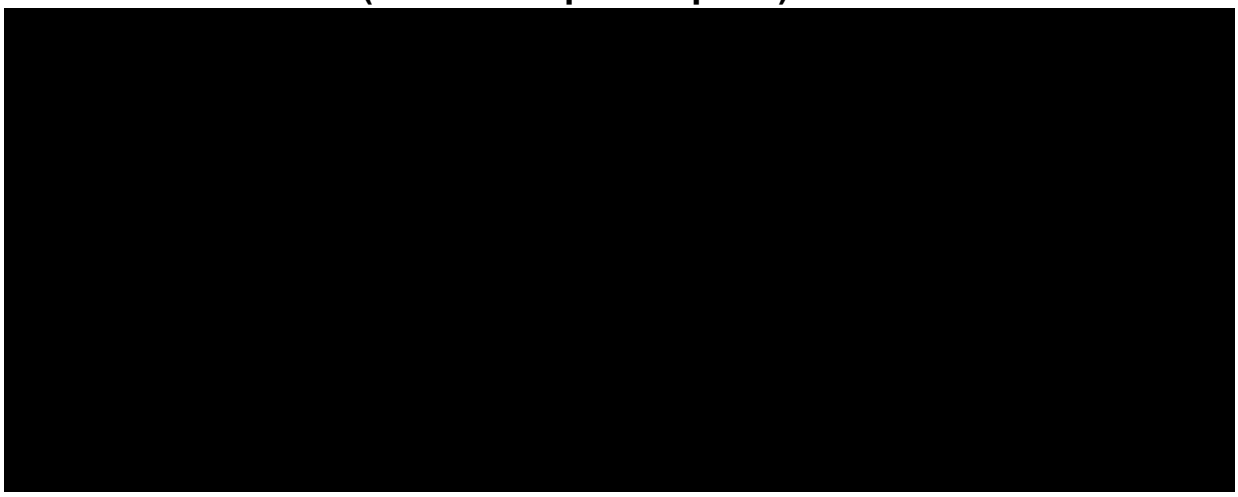
12 Protocol adherence

Investigators ascertain they will apply due diligence to avoid protocol deviations. Under no circumstances should the investigator contact Novartis or its agents, if any, monitoring the study to request approval of a protocol deviation, as no authorized deviations are permitted. If the investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC/REB it cannot be implemented. All significant protocol deviations will be recorded and reported in the CSR.

12.1 Amendments to the protocol

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, Health Authorities where required, and the IRB/IEC/REB. Only amendments that are required for patient safety may be implemented prior to IRB/IEC/REB approval. Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any patient included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis should be notified of this action and the IRB/IEC at the study site should be informed according to local regulations (e.g. UK requires the notification of urgent safety measures within 3 days) but not later than 10 working days.

13 References (available upon request)



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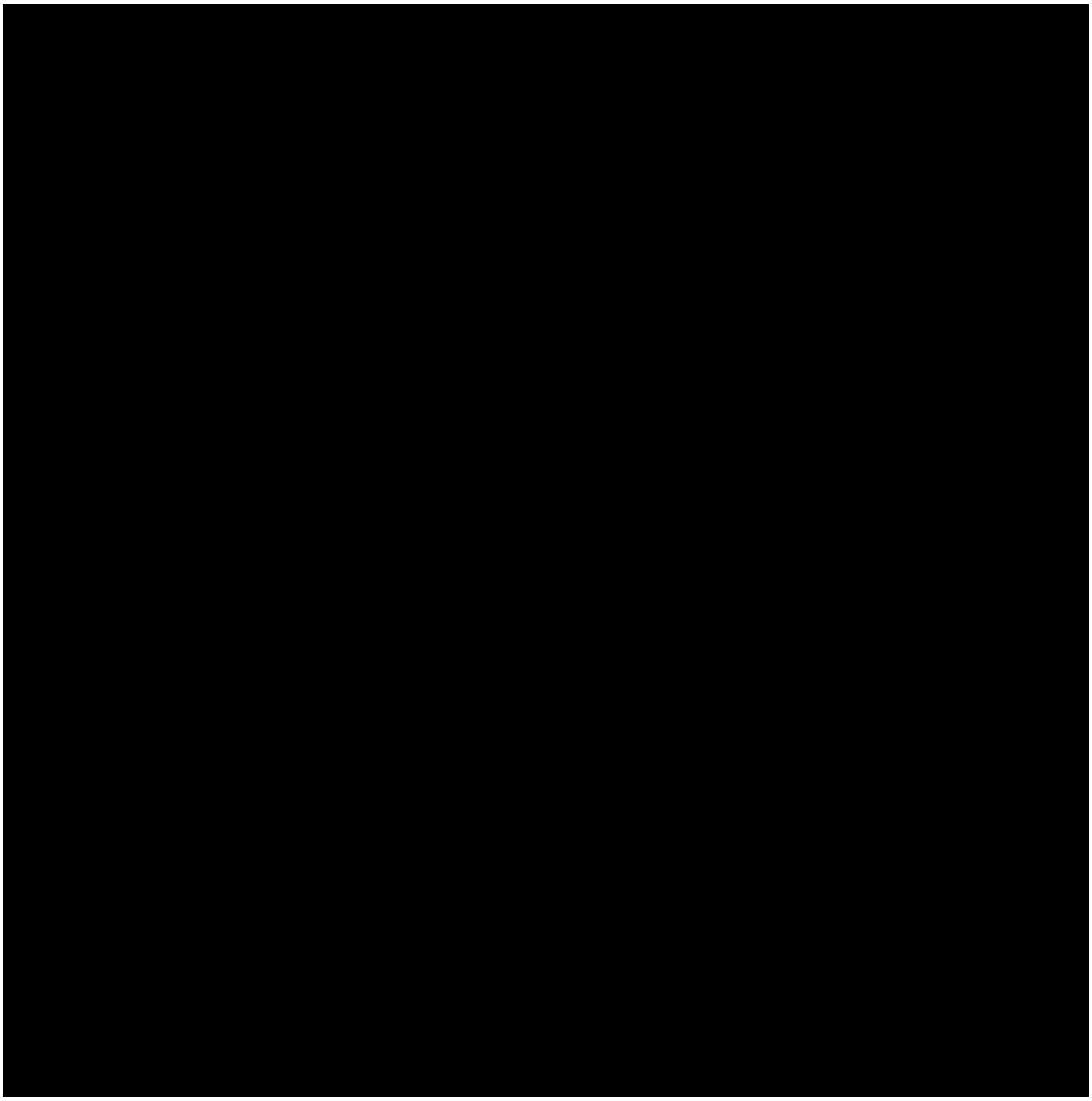
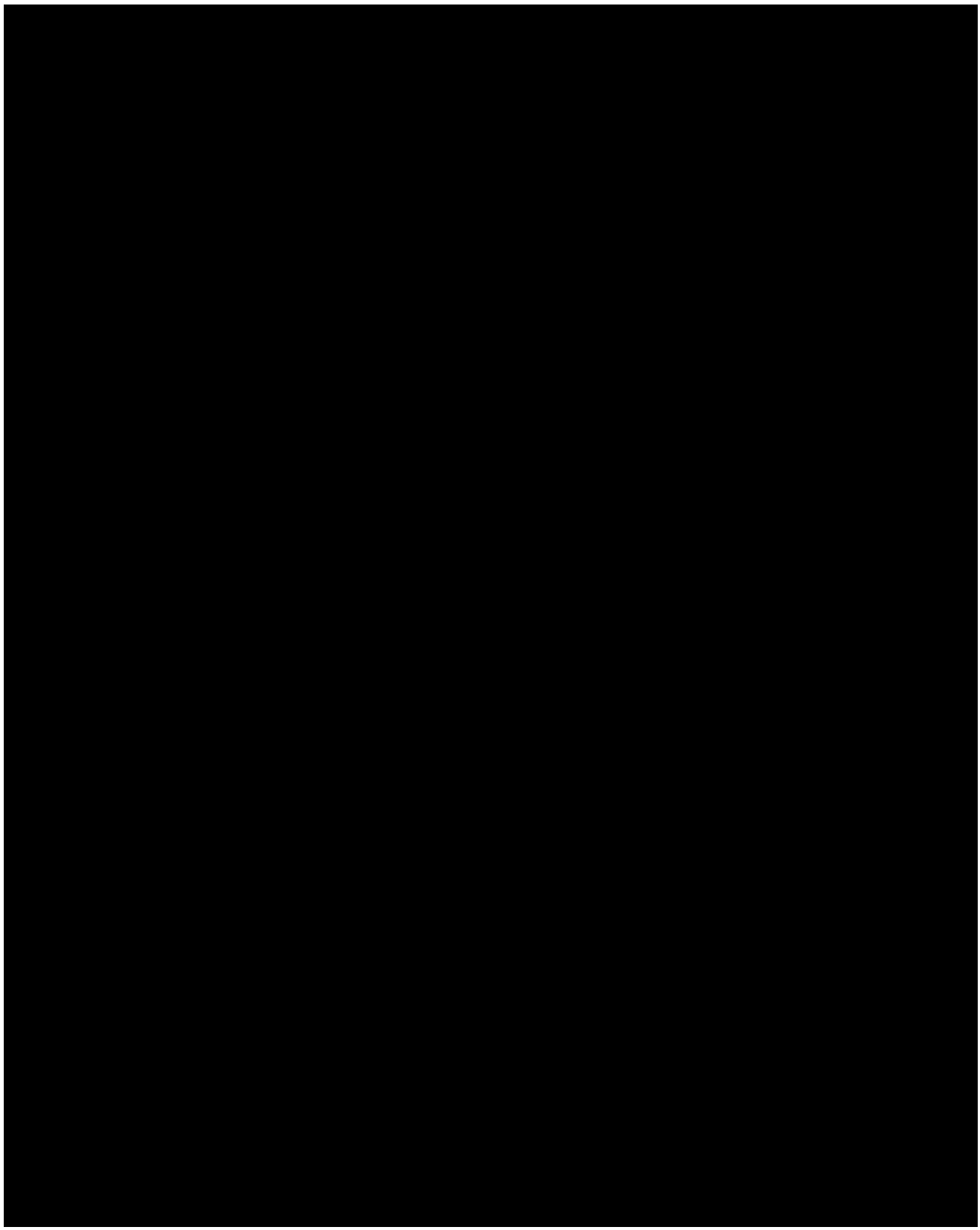
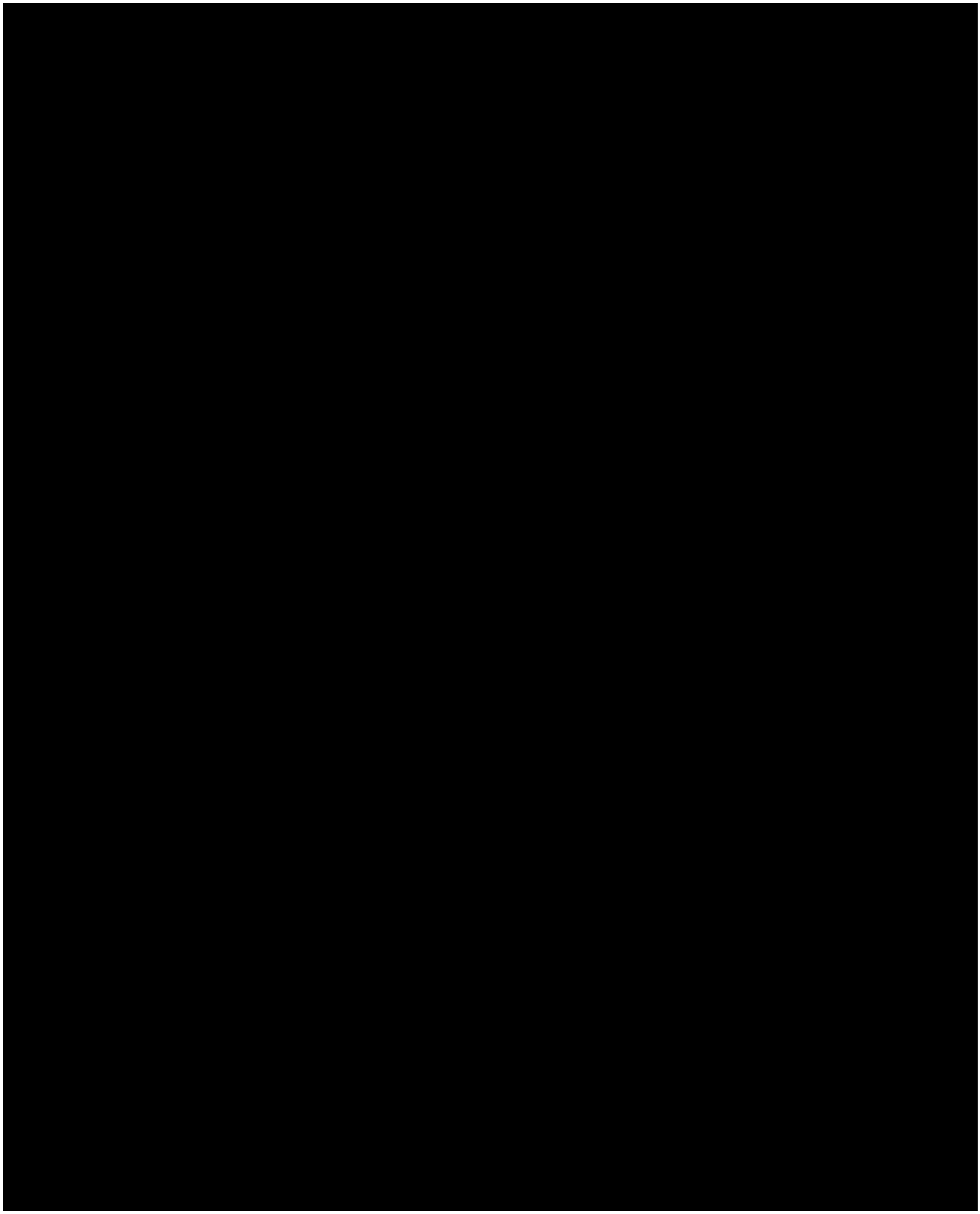
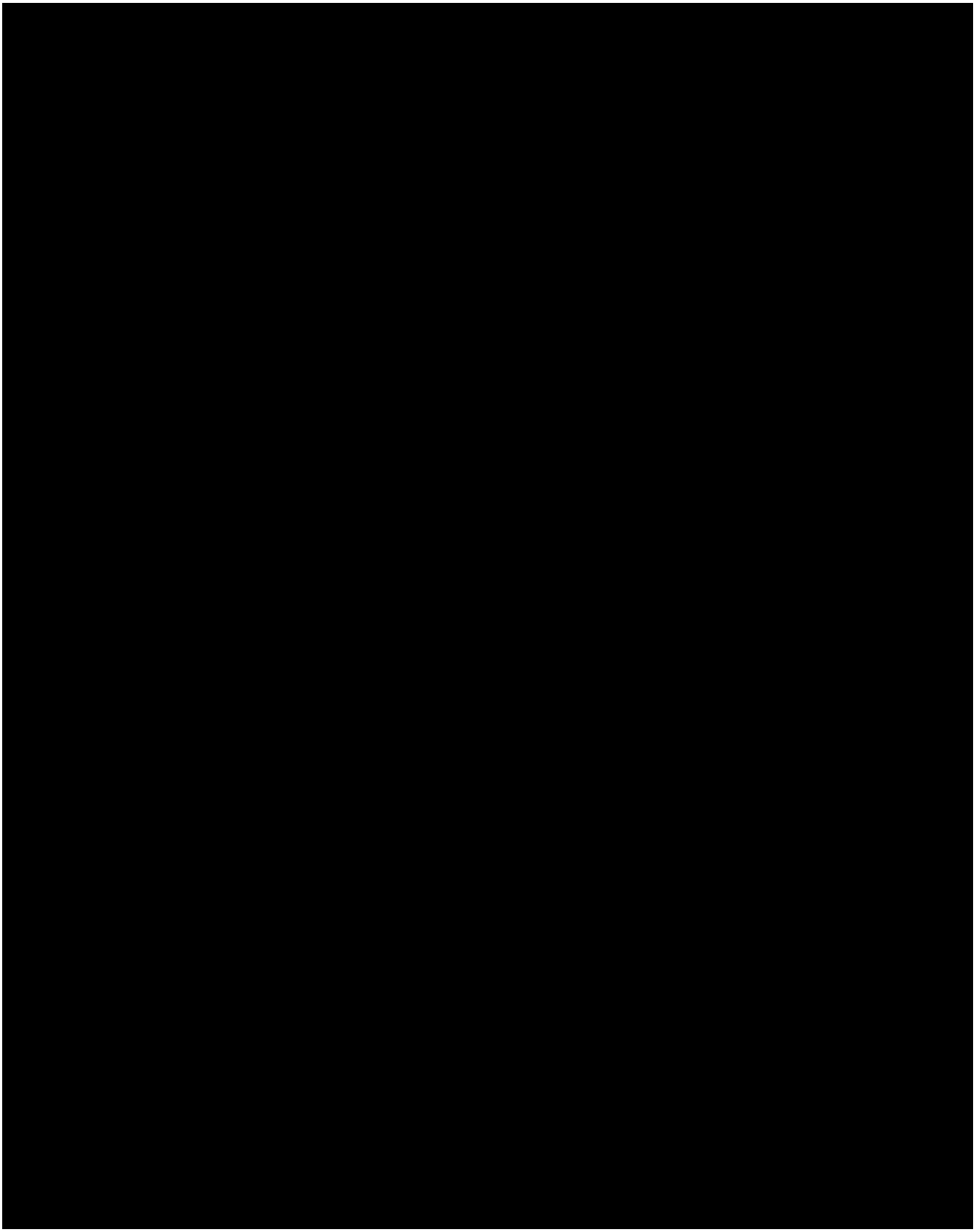
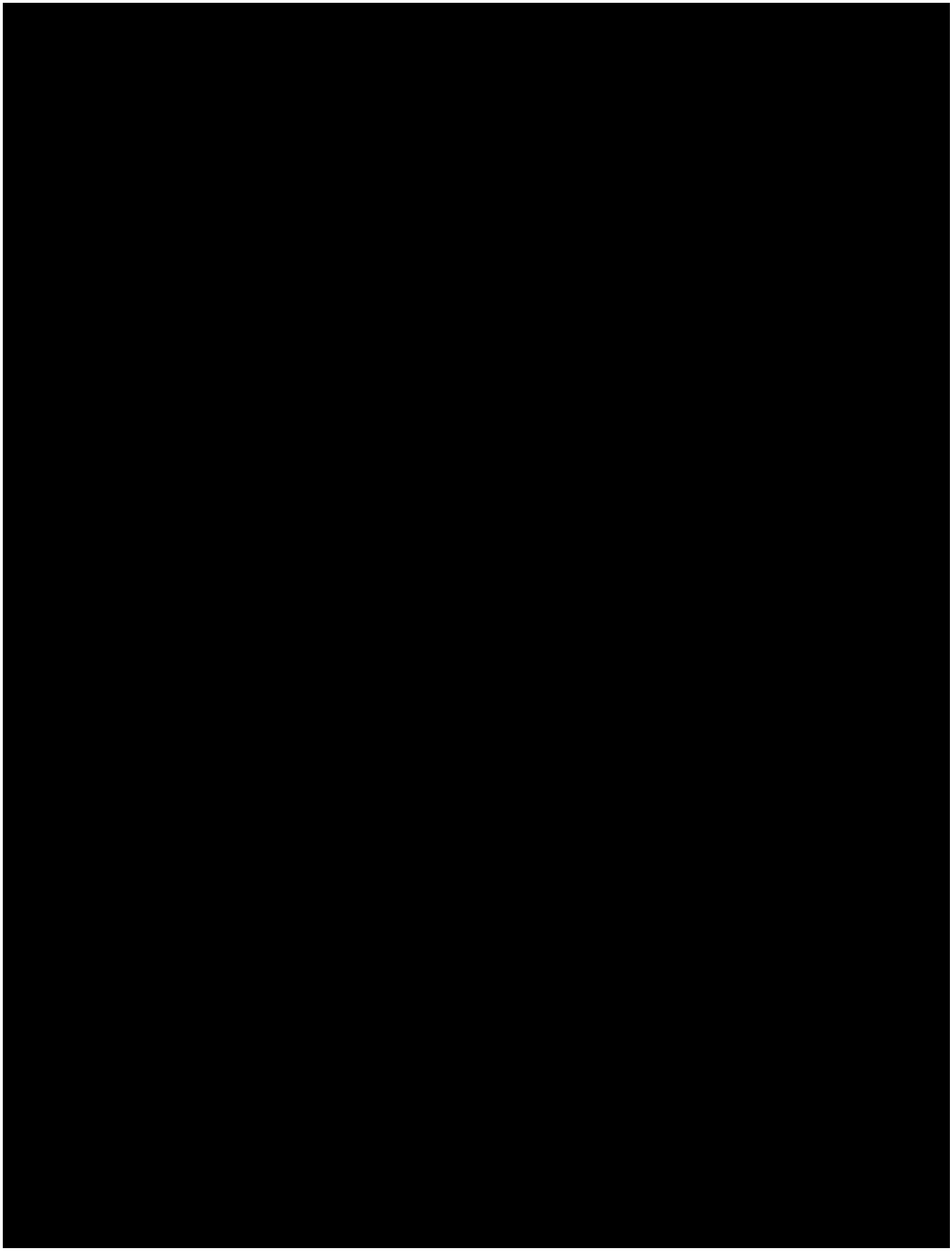
14 Appendices

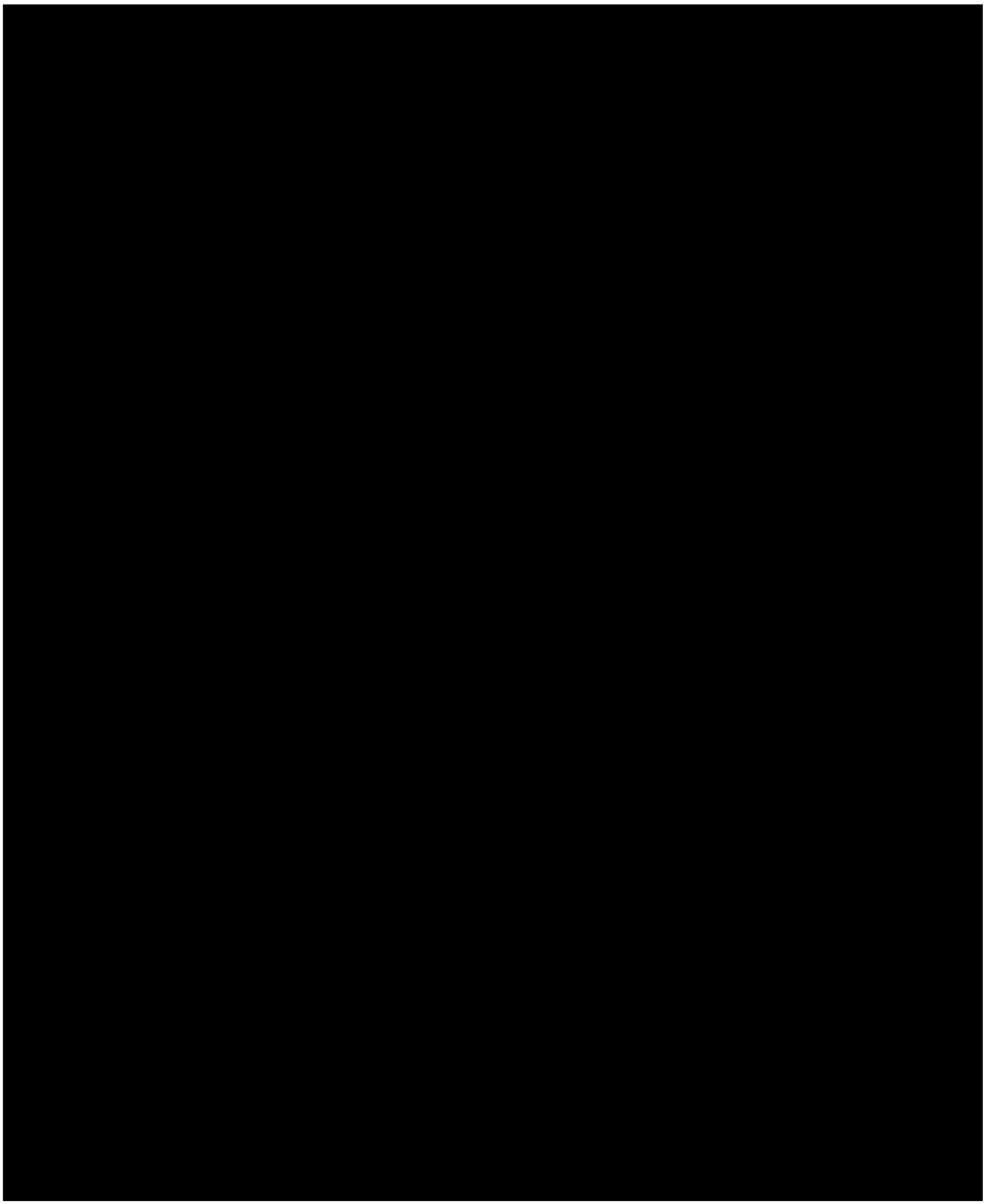


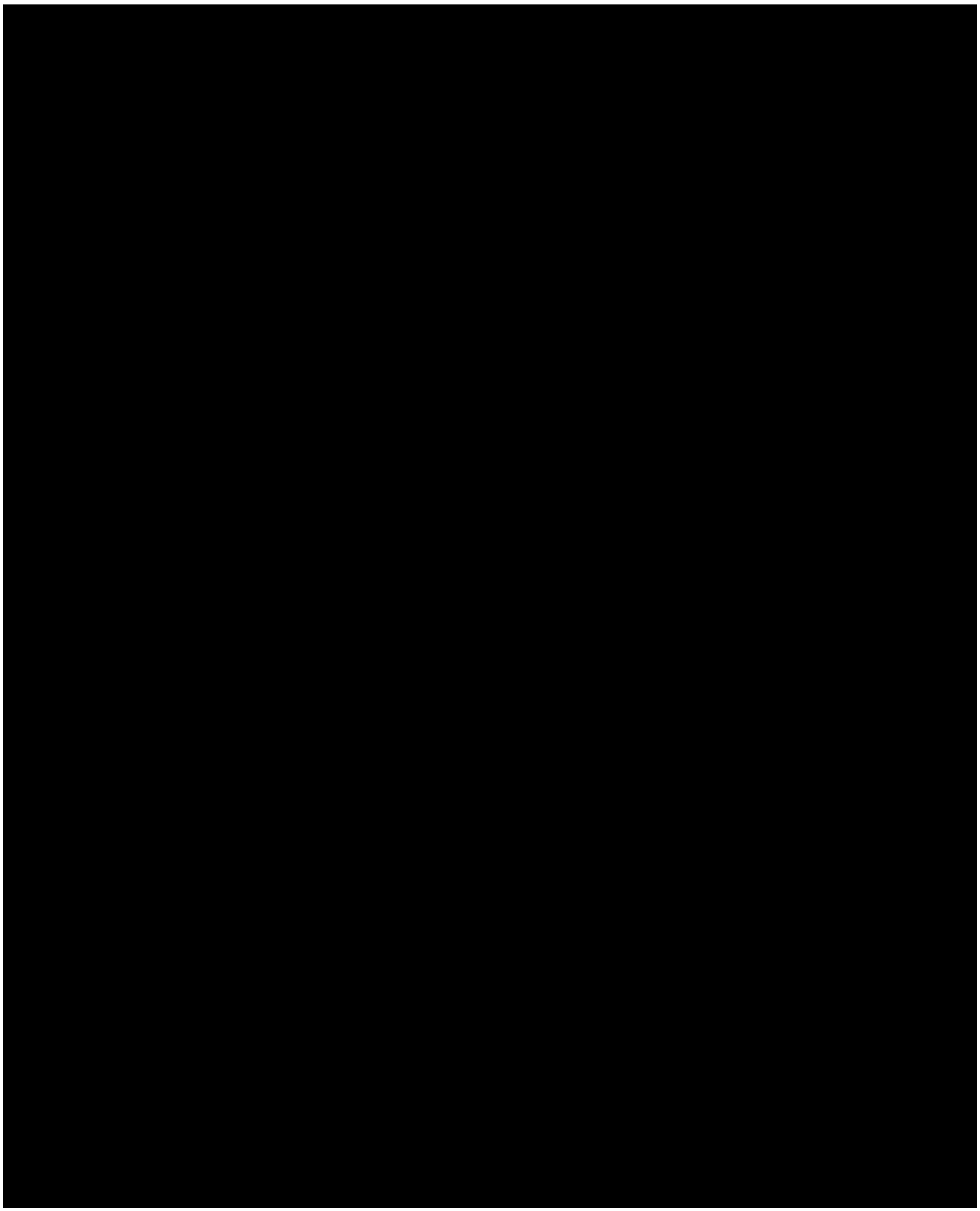


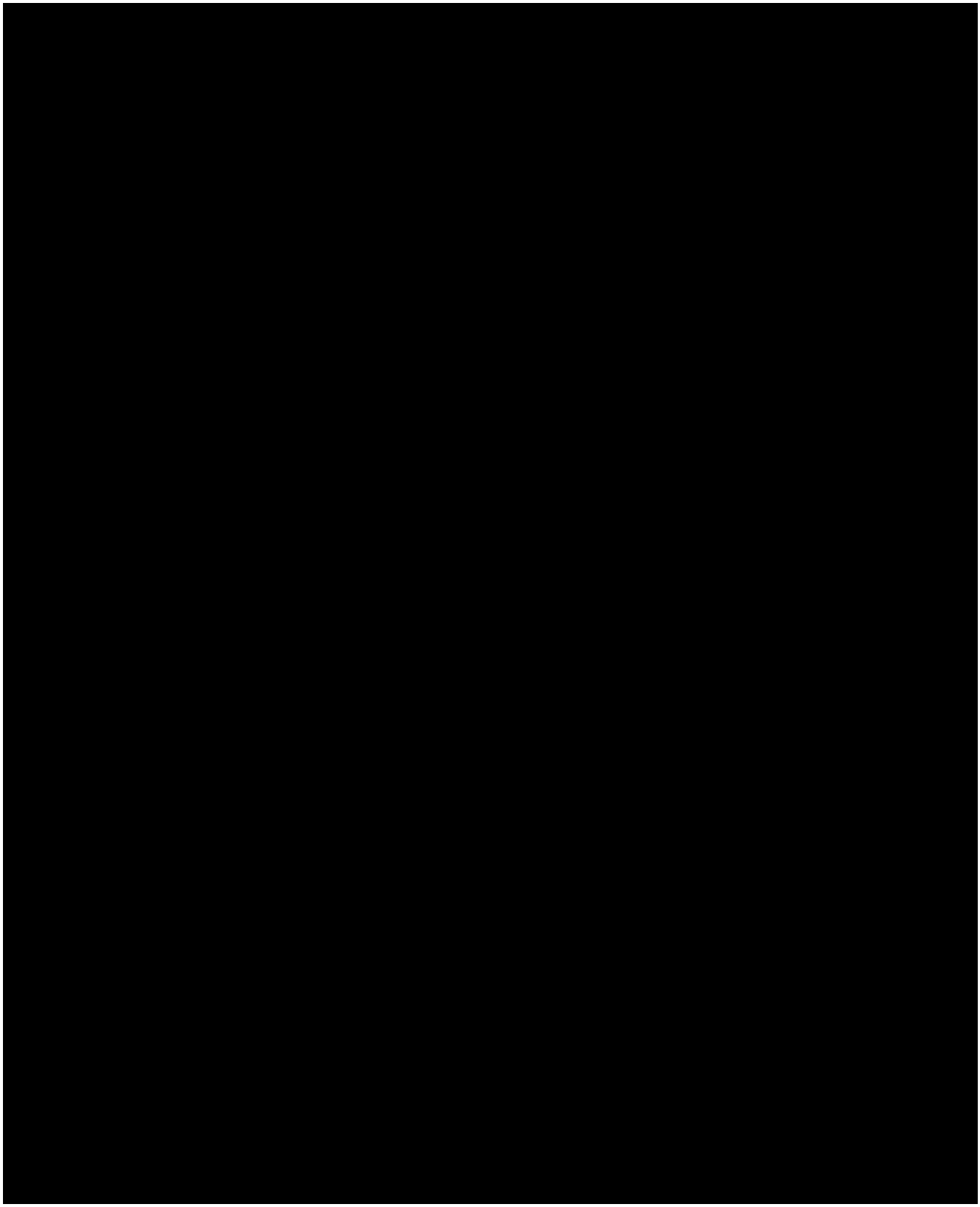


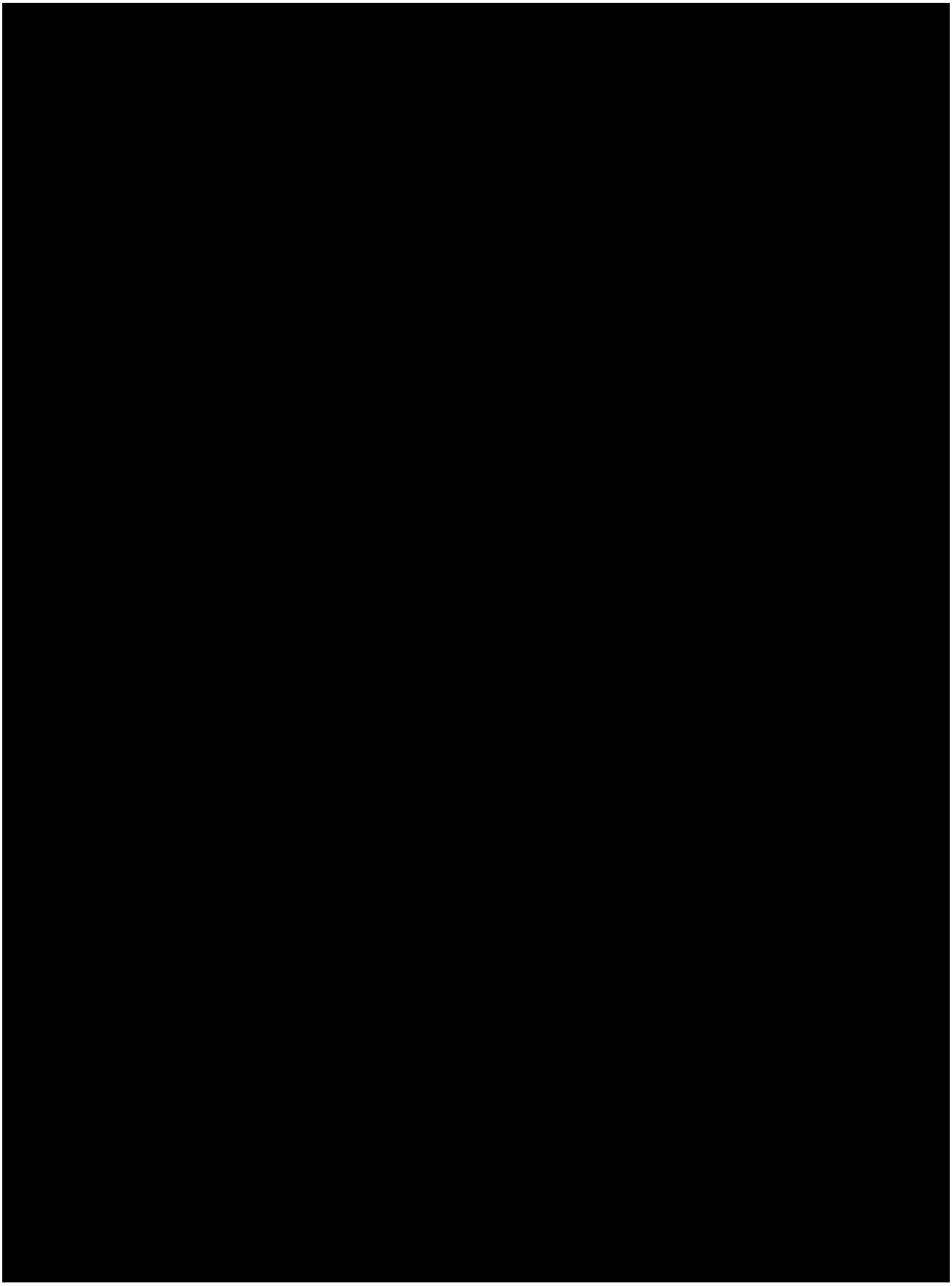


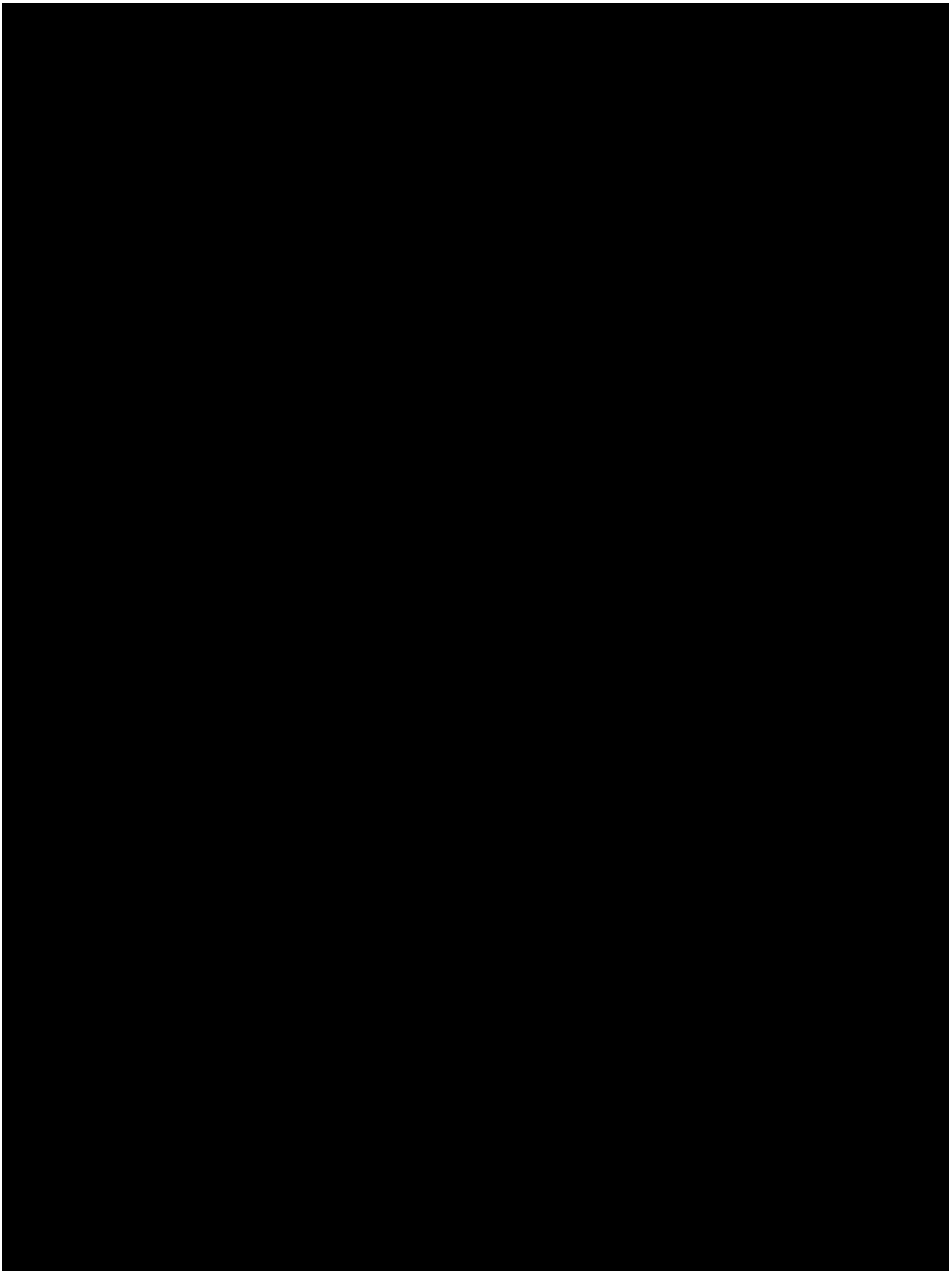


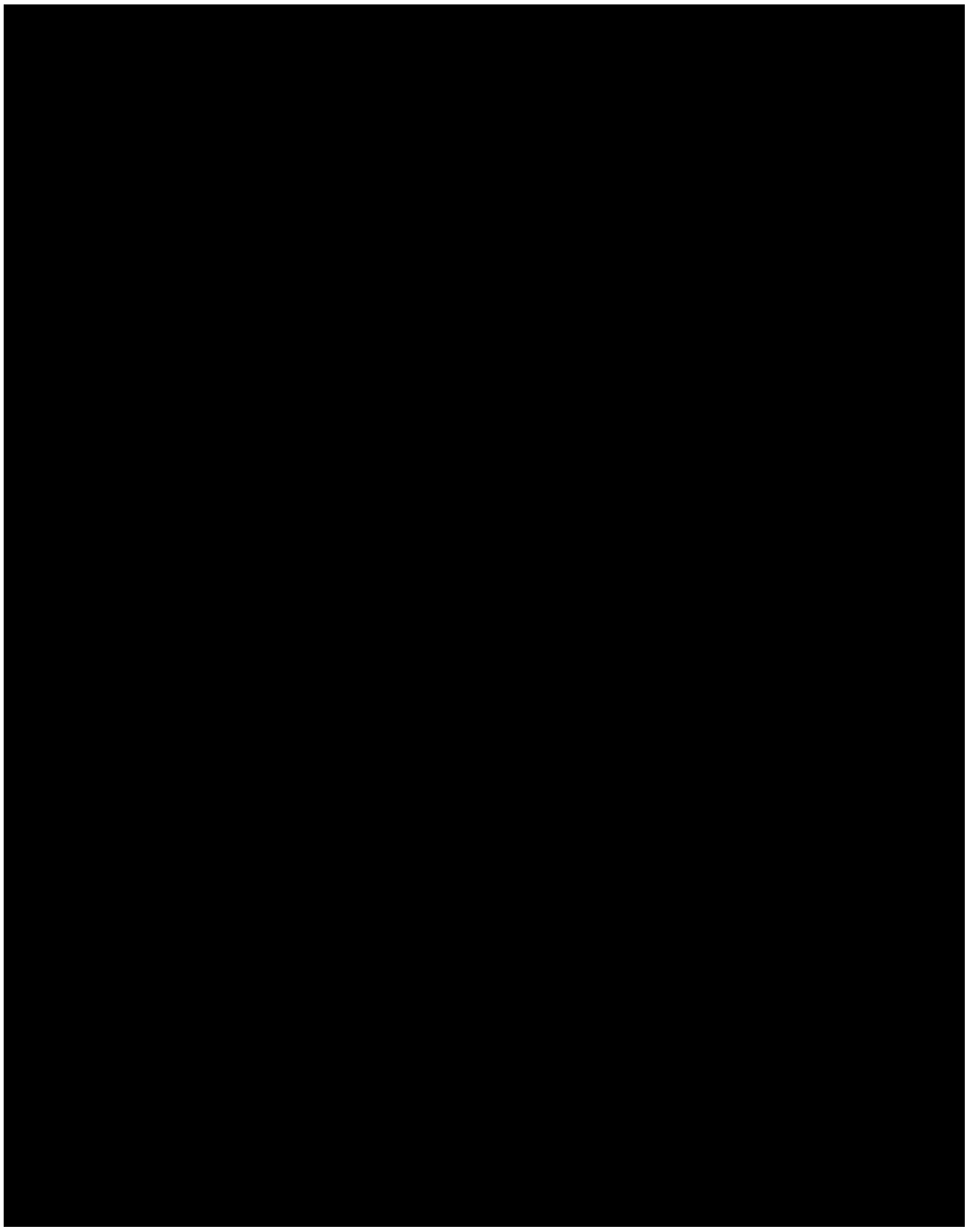


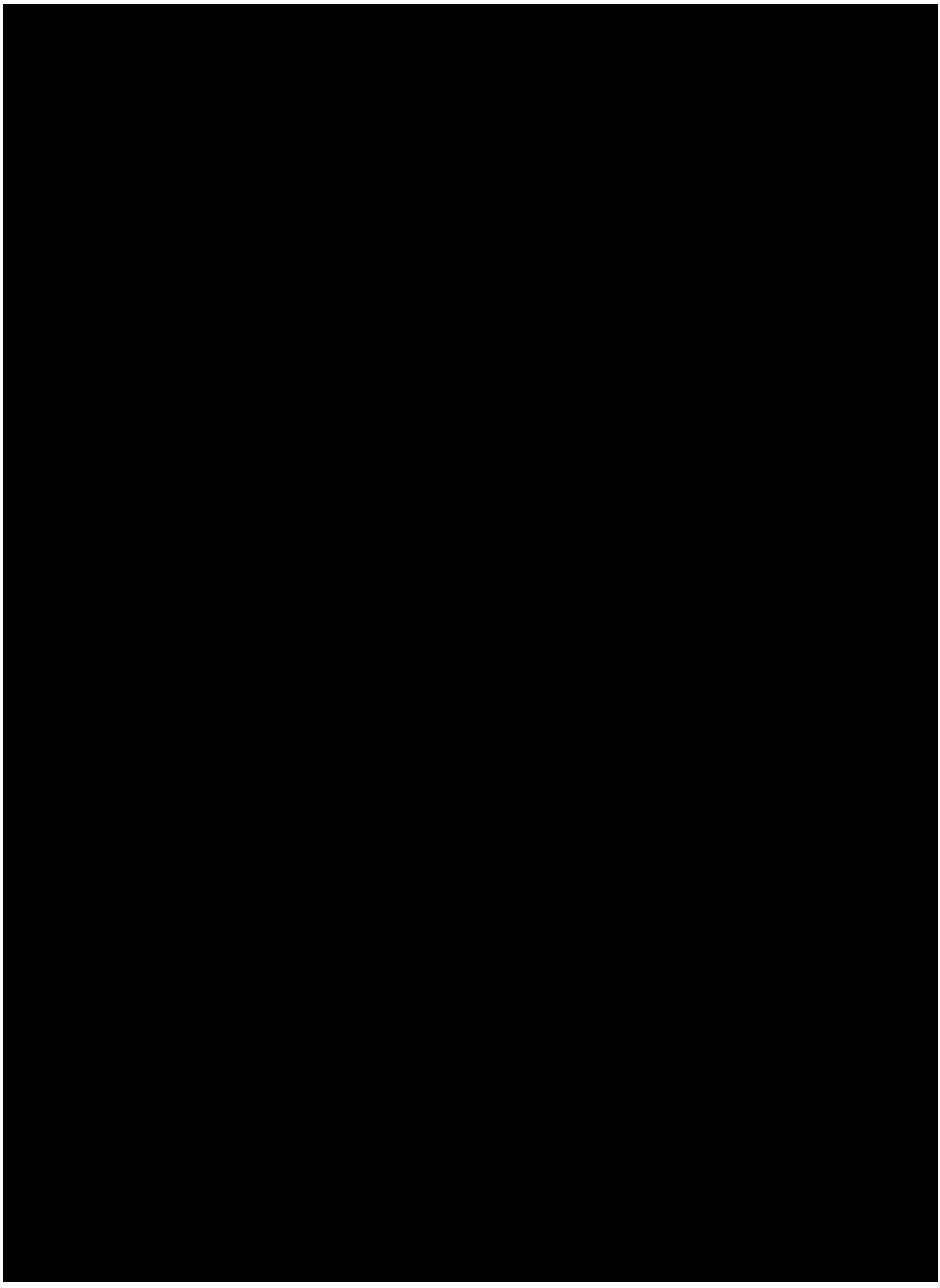


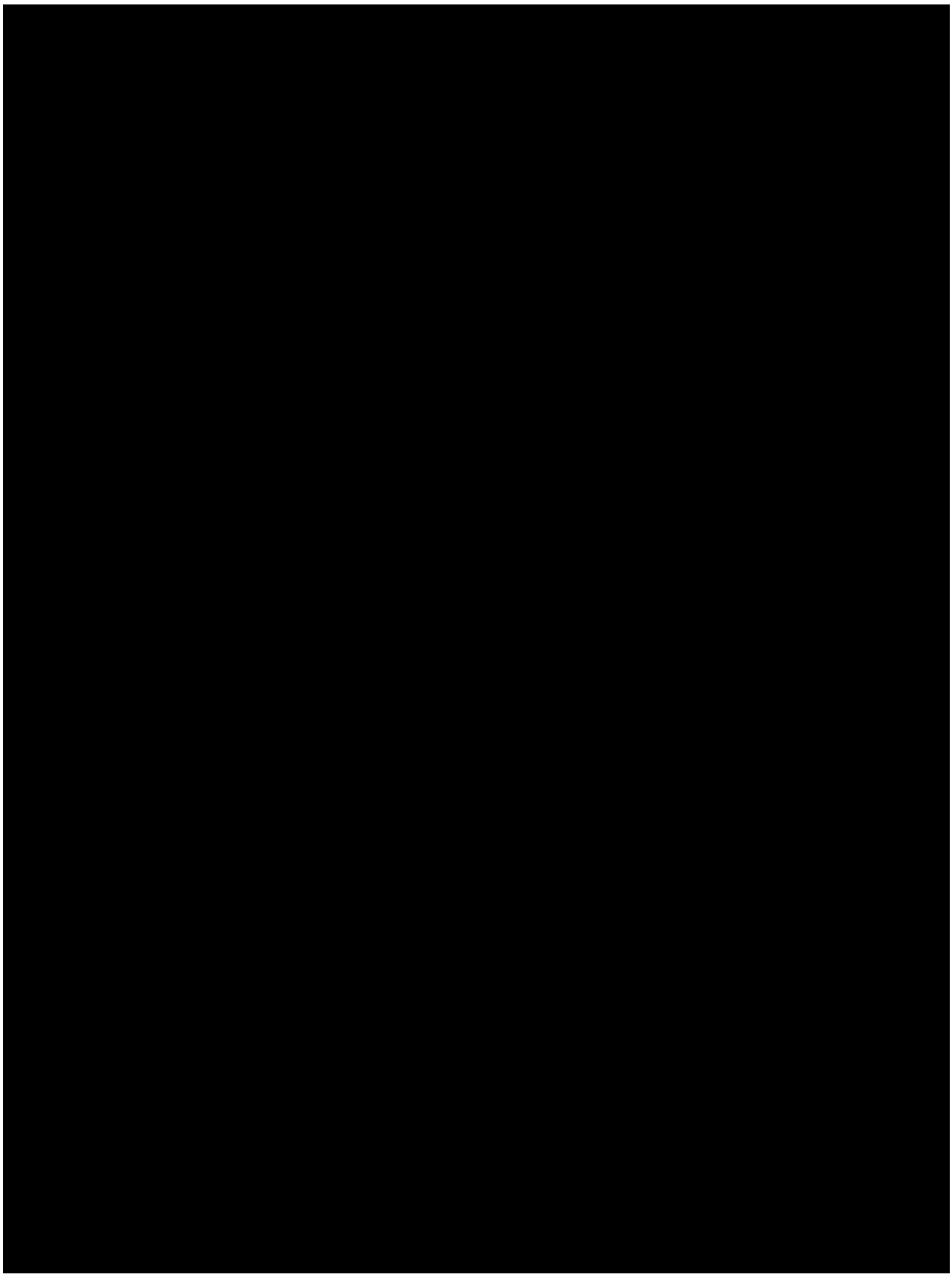


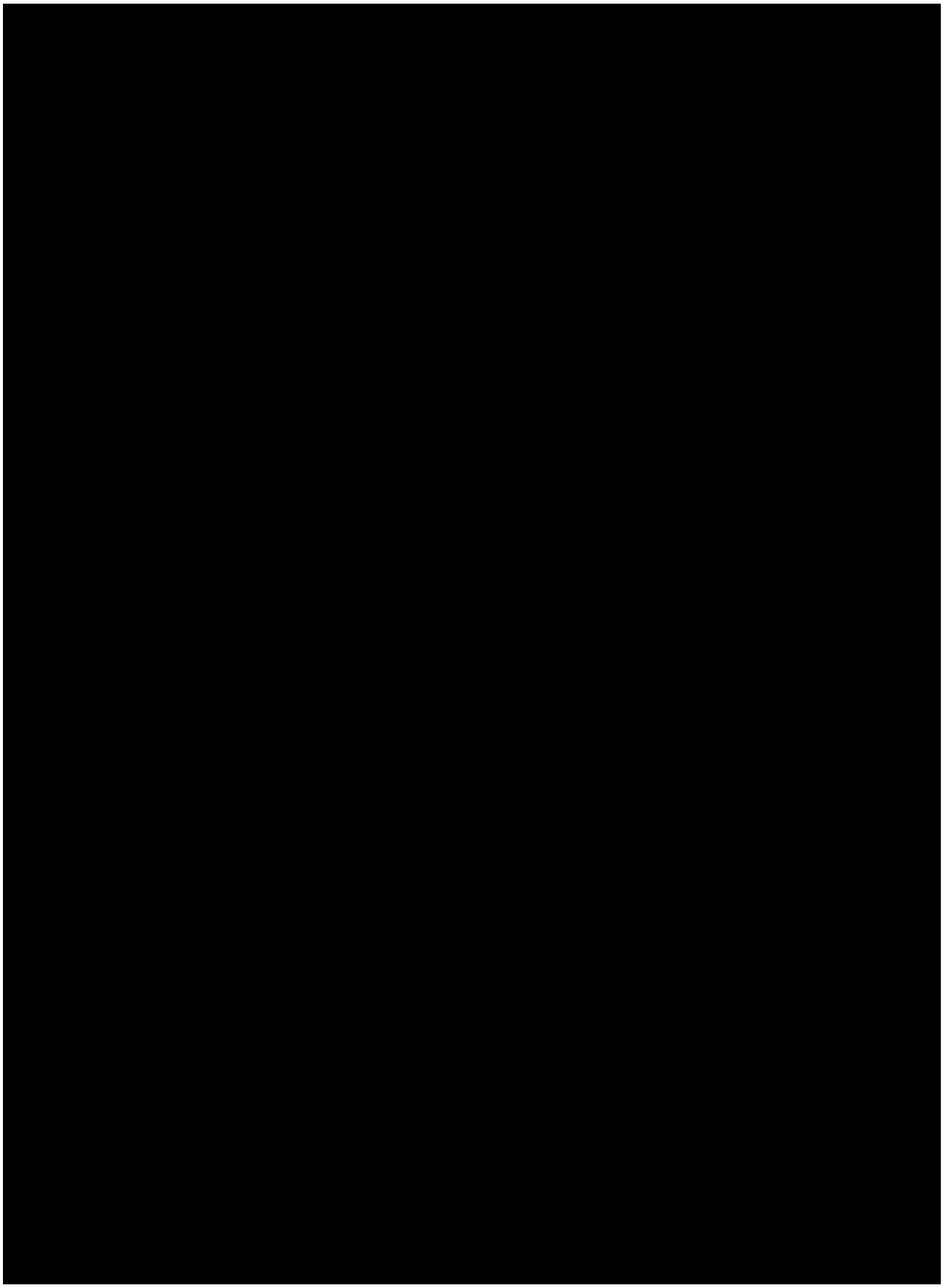


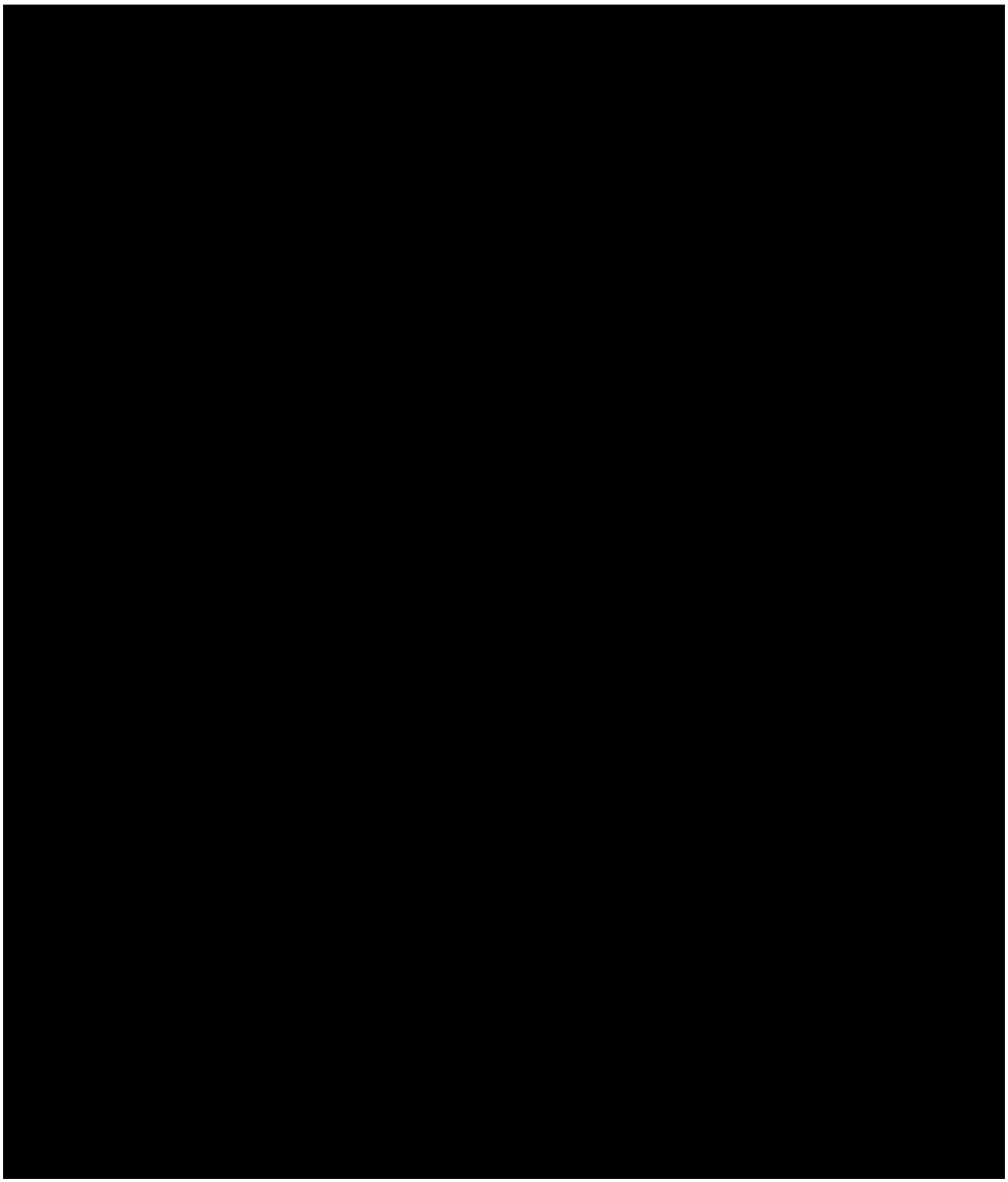


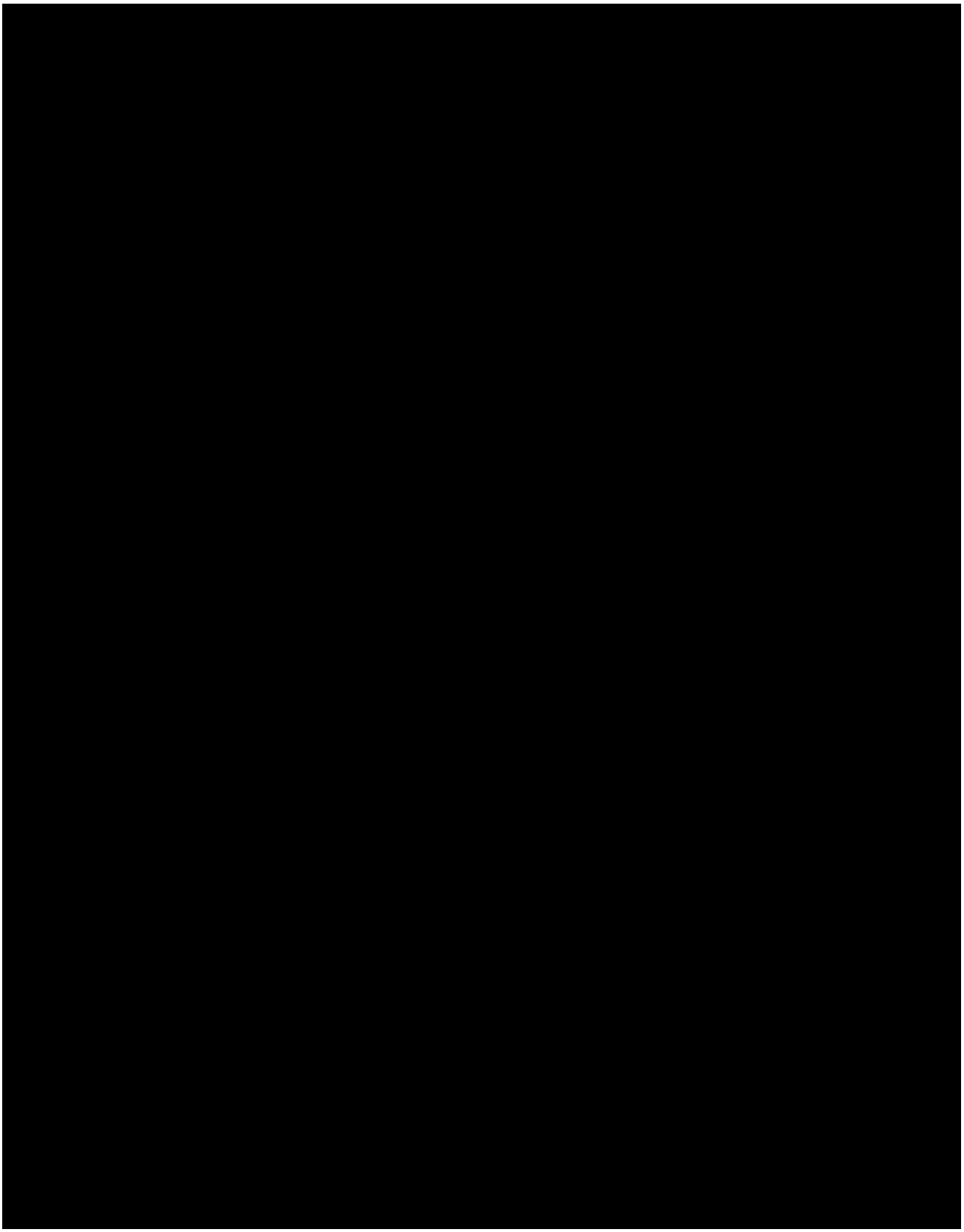


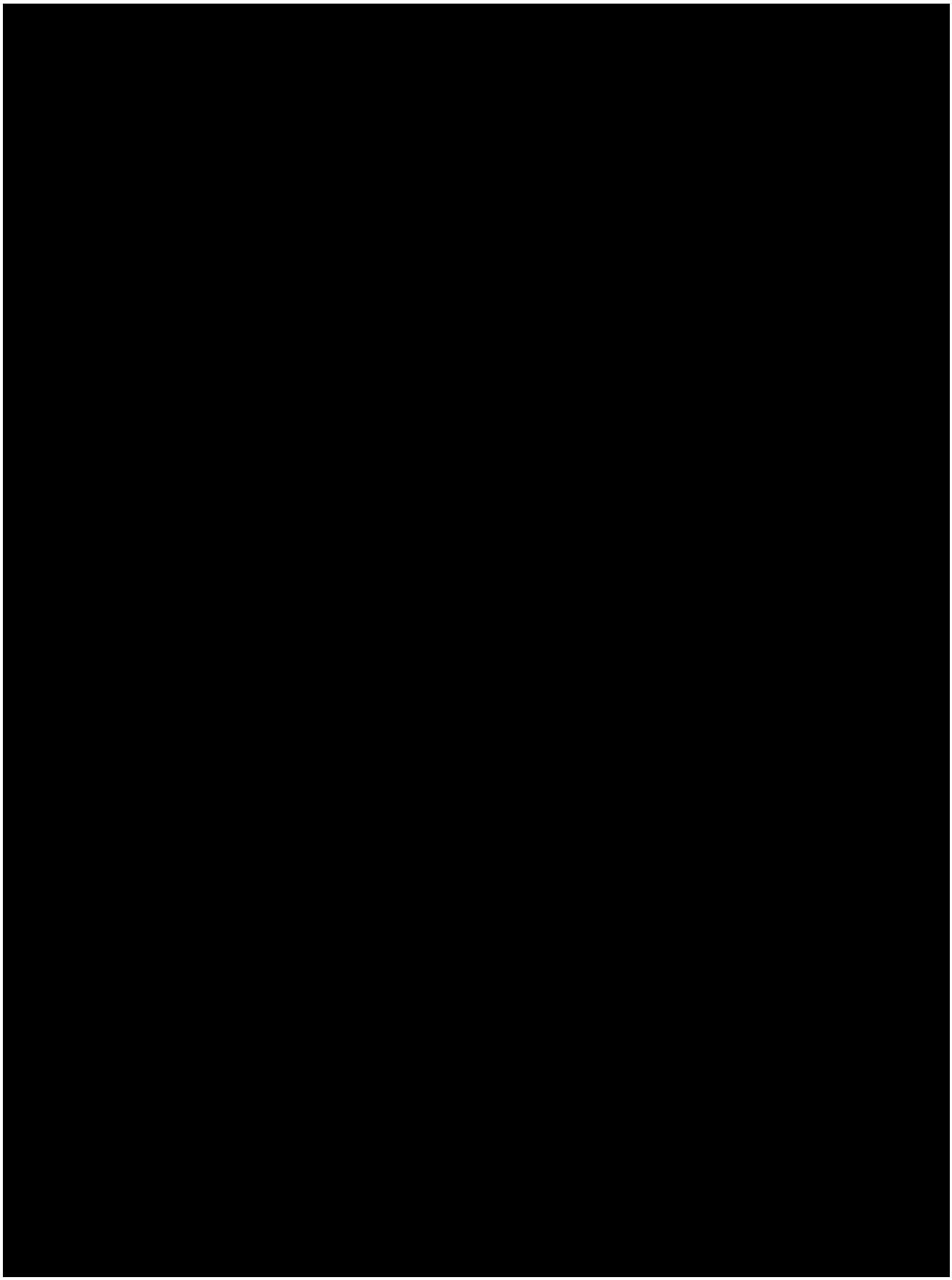


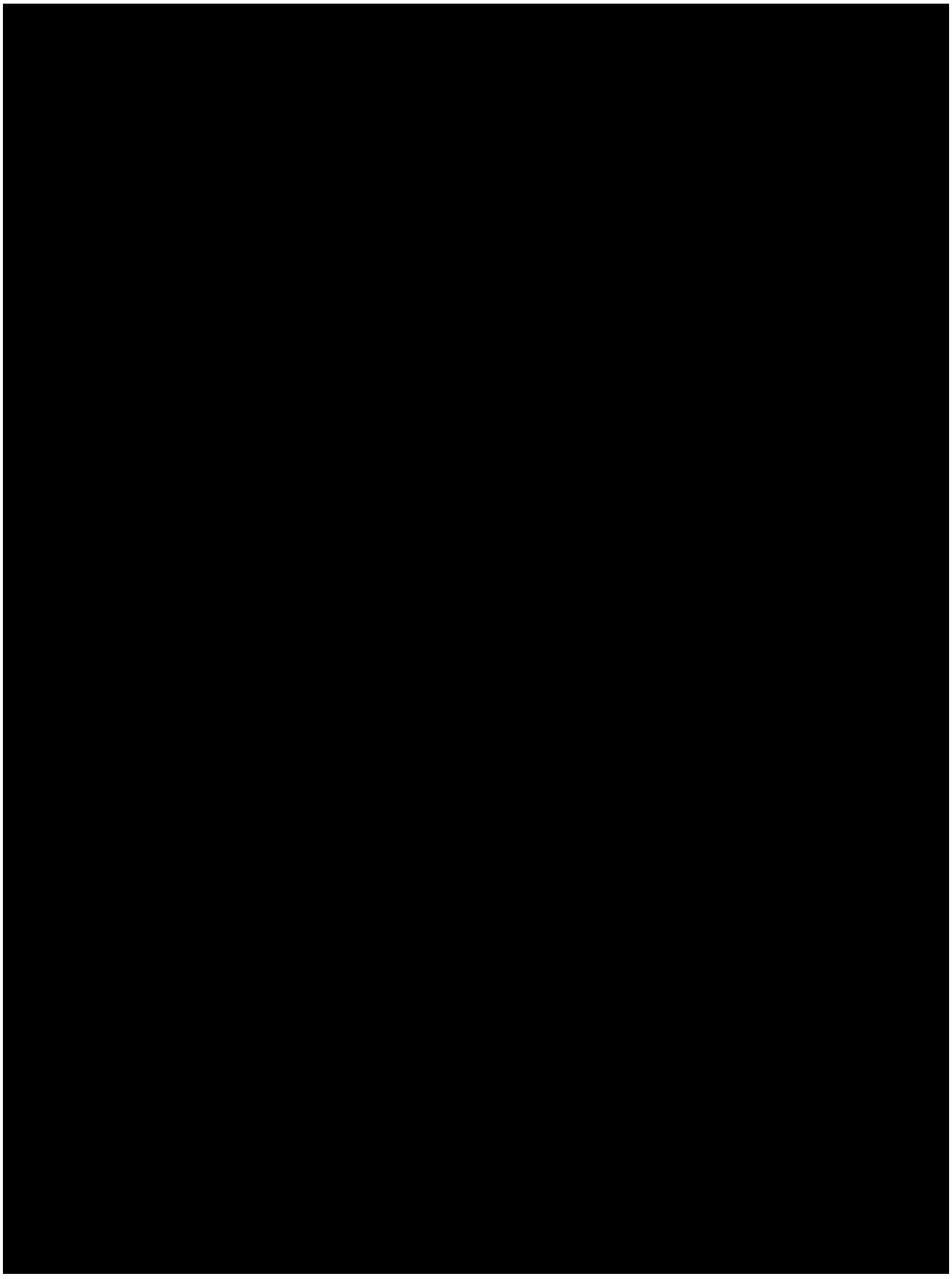


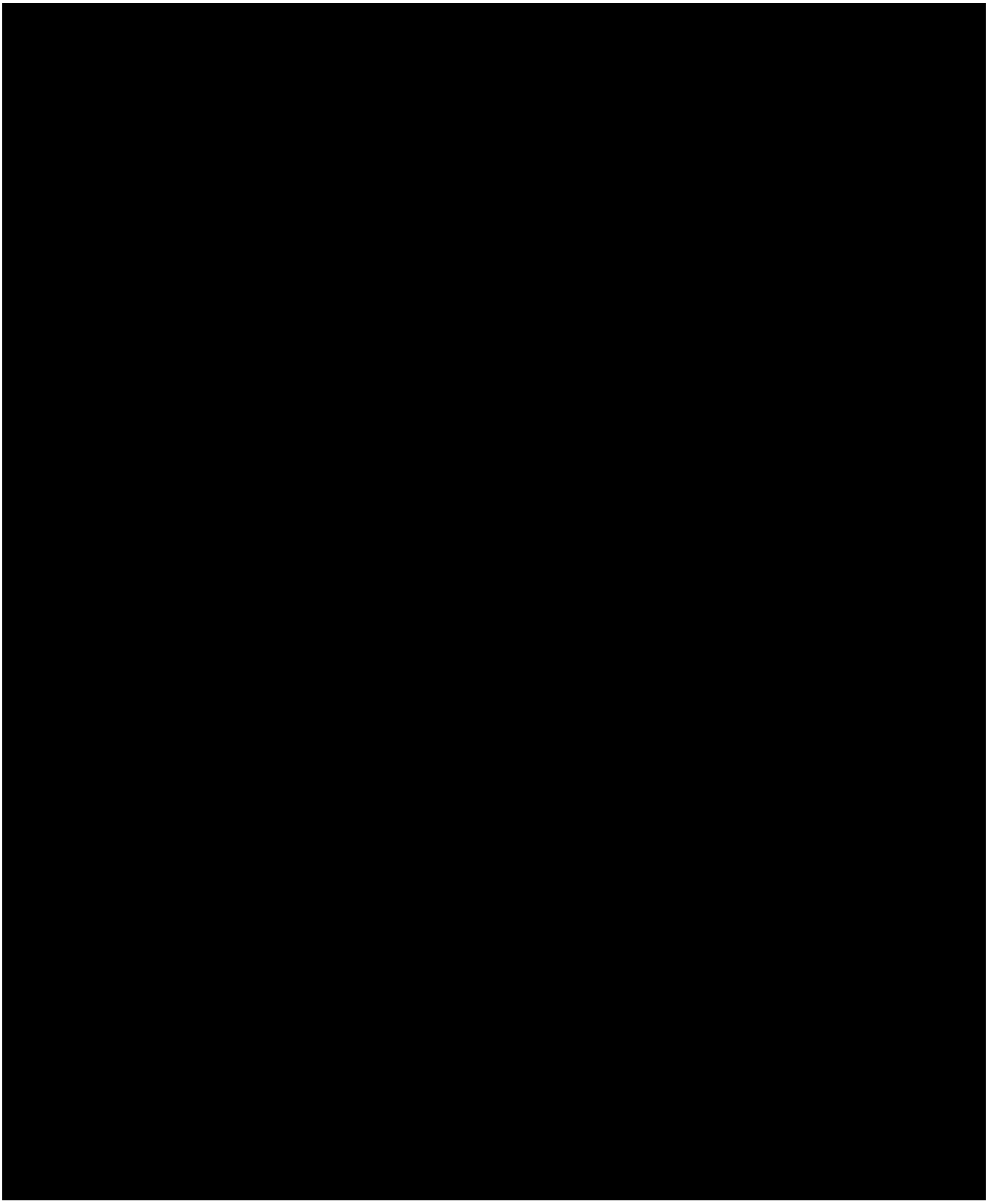


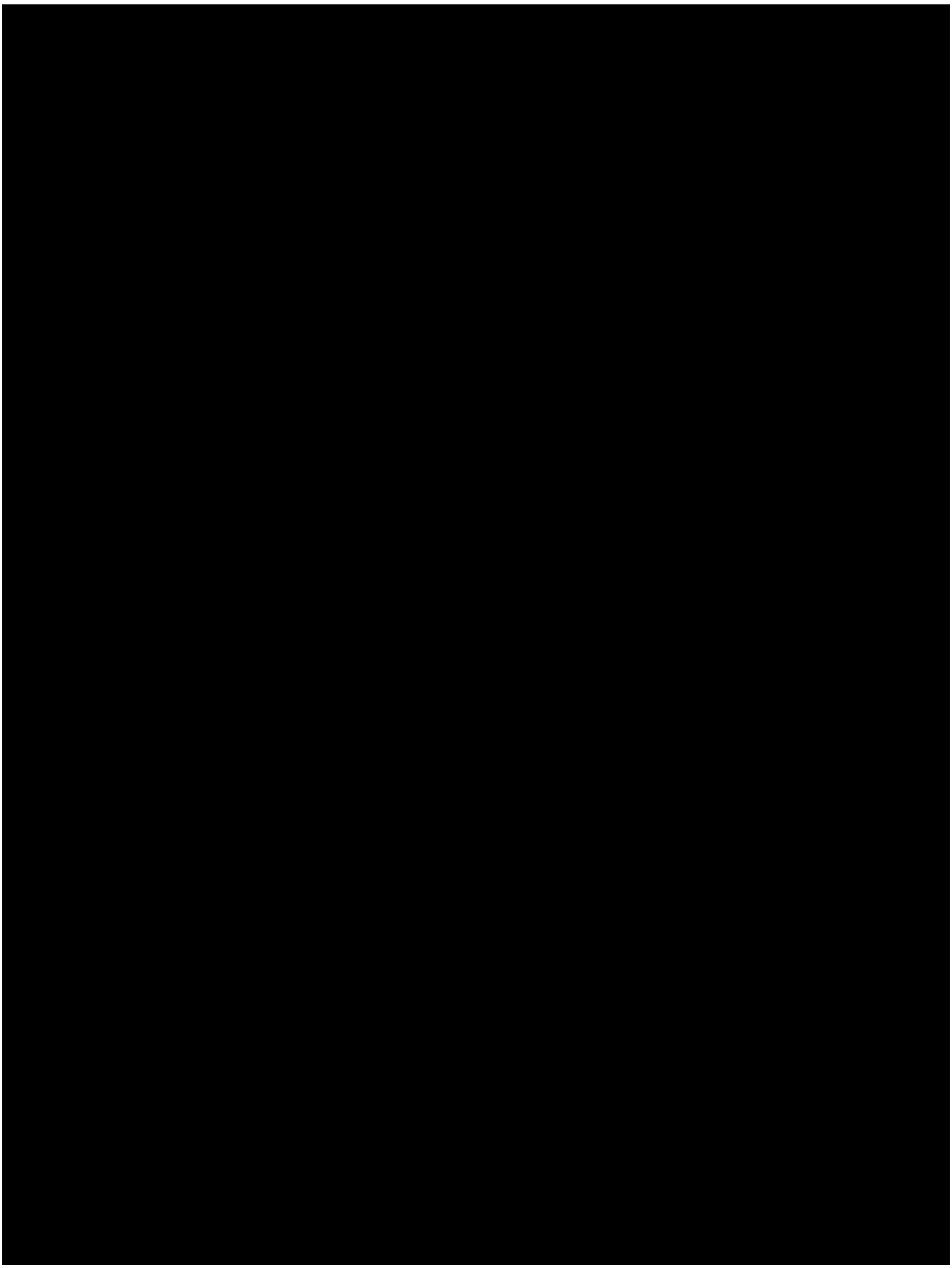


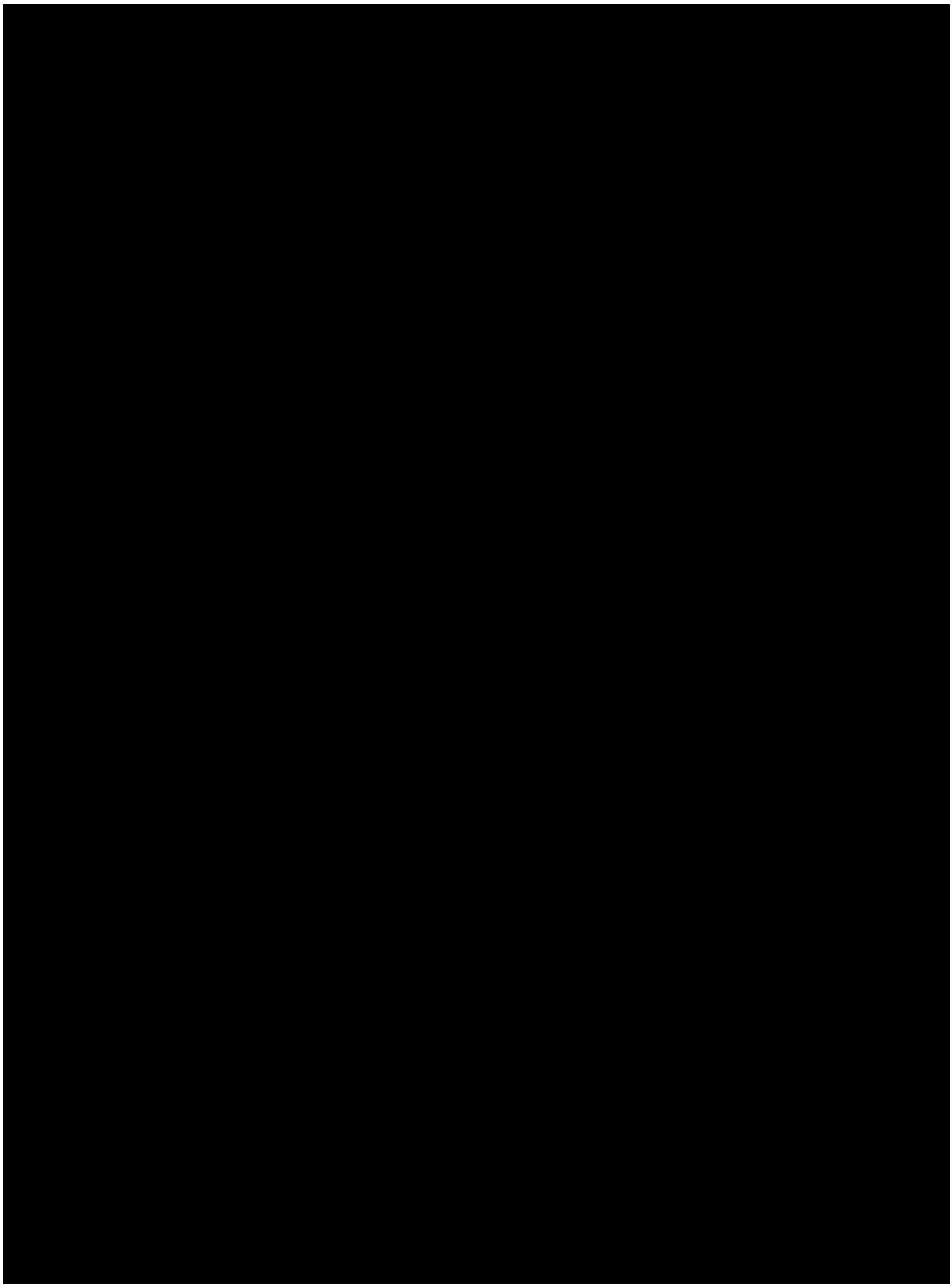


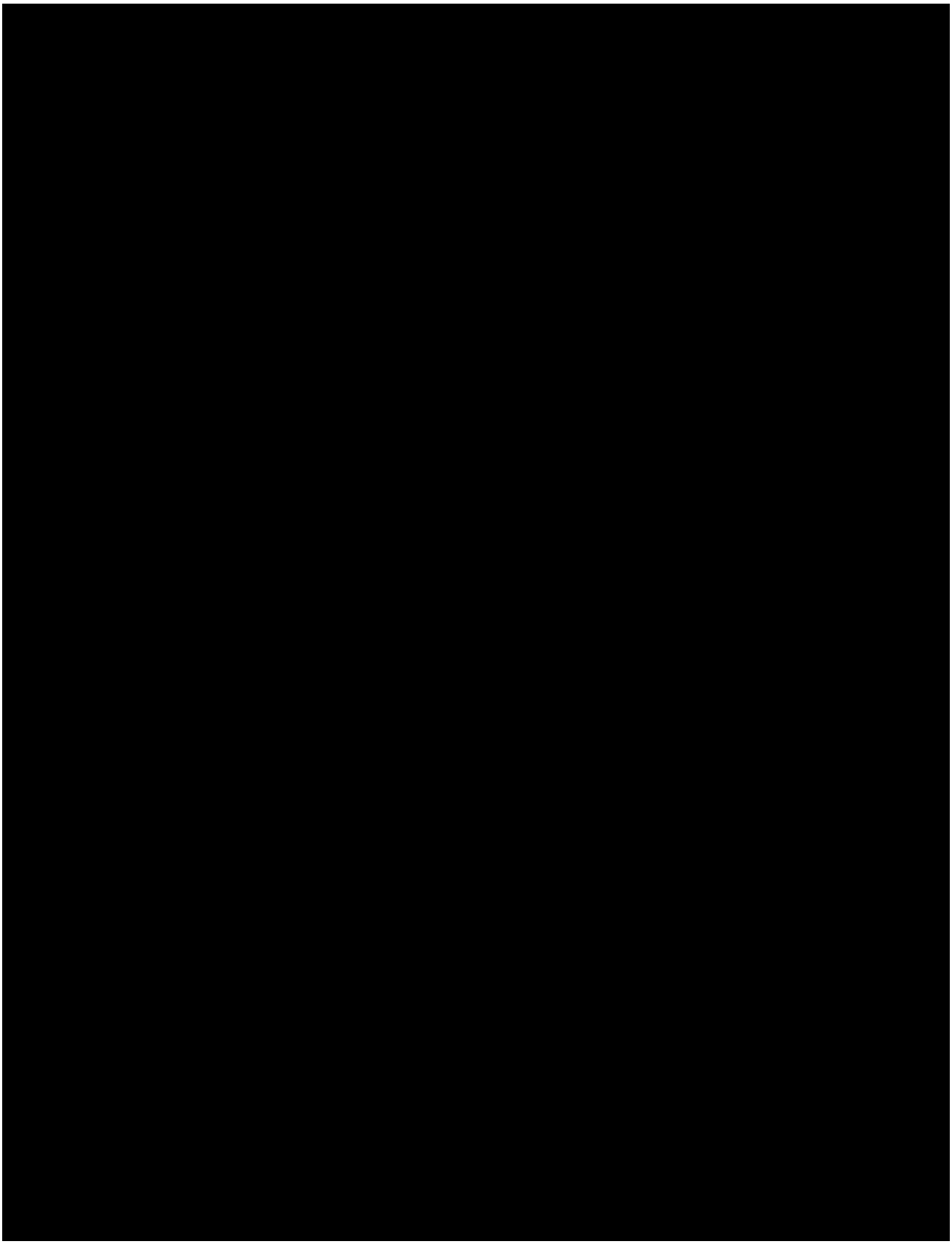


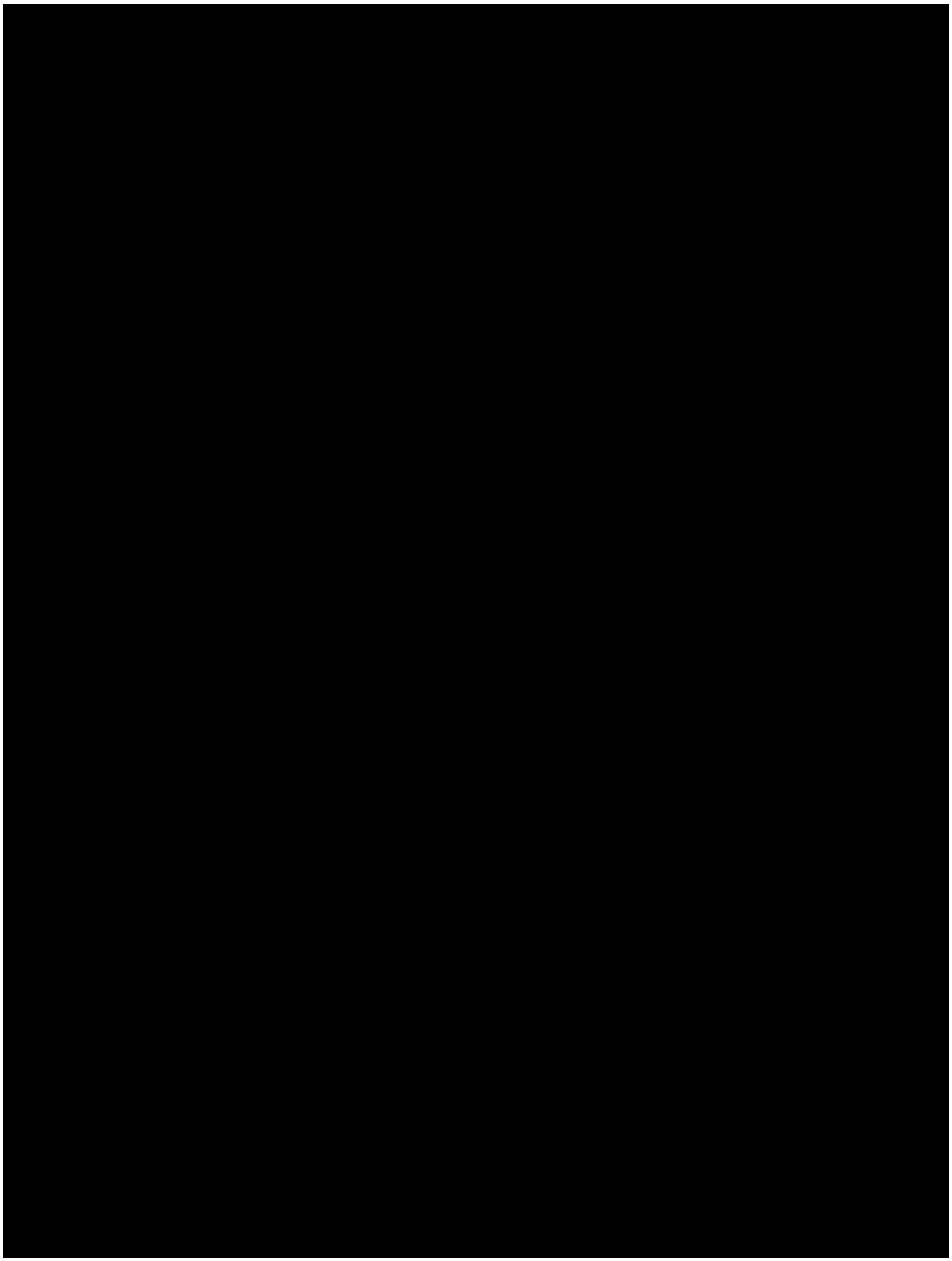












14.2 Appendix 2: Drugs that are prohibited or to be used with caution

In general, the use of any concomitant medication deemed necessary for the care of the patient is permitted in this study, except as specifically prohibited below. Combination administration of study drugs could result in drug-drug interactions (DDI) that could potentially lead to reduced activity or enhanced toxicity of the concomitant medication and/or LTT462.

The following lists are based on the Oncology Clinical Pharmacology Drug-Drug Interaction memo (released in April 2015). The FDA's Guidance for Industry, Drug Interaction Studies - Study Design, Data Analysis and Implications for Dosing and Labeling (February 2012), is the basis of the OCP DDI List, and it was supplemented with the data from the Indiana University School of Medicine's "Clinically Relevant" Table and the University of Washington's Drug Interaction Database.

The list of medications in Table 14-6 and Table 14-7 is meant to provide guidance and it is not a comprehensive list. If the patient requires to take a medication that is not in the list, but there might be a risk of DDI, please contact Novartis.

If a drug appears in Table 14-6 (prohibited) as well as in Table 14-7 (drugs to be used with caution), the drug should be considered as prohibited.

Please contact the Novartis Medical monitor with any questions.

Table 14-6 Drugs prohibited while on study

Category	Drug Names
[redacted]	
Proton pump Inhibitor	Omeprazole, lansoprazole, dexlansoprazole, esomeprazole, pantoprazol, rabeprazole

Category	Drug Names
[redacted]	

Table 14-7 Drugs to be used with caution while on study

Category	Drug Names
[redacted]	

In the event that a drug appears in both the listings of prohibited and drugs to be used with caution, the drug is prohibited.

1 LTT462 should be administered at least 1 hour before or 2 hours after an antacid

2 LTT462 should be administered at least 3 hours before or 6 hours after an H2 receptor antagonist.

[redacted]